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(54) Title: MODIFICATION OF FEEDING BEHAVIOR

(57) Abstract: Methods are disclosed for decreasing calorie intake, food intake, and appetite in a subject. The methods include peripherally administering a therapeutically effective amount of PYY or an agonist thereof to the subject, thereby decreasing the calorie intake of the subject.

believed to contribute. In general, obesity has been described as a condition in which excess body fat puts an individual at a health risk.

There is strong evidence that obesity is associated with increased morbidity and mortality. Disease risk, such as cardiovascular disease risk and type 2 diabetes disease risk, increases independently with increased body mass index (BMI). Indeed, this risk has been quantified as a five percent increase in the risk of cardiac disease for females, and a seven percent increase in the risk of cardiac disease for males, for each point of a BMI greater than 24.9 (see Kenchaiah et al., *N. Engl. J. Med.* 347:305, 2002; Massie, *N. Engl. J. Med.* 347:358, 2002). In addition, there is substantial evidence that weight loss in obese persons reduces important disease risk factors. Even a small weight loss, such as 10% of the initial body weight in both overweight and obese adults has been associated with a decrease in risk factors such as hypertension, hyperlipidemia, and hyperglycemia.

Although diet and exercise provide a simple process to decrease weight gain, overweight and obese individuals often cannot sufficiently control these factors to effectively lose weight. Pharmacotherapy is available; several weight loss drugs have been approved by the Food and Drug Administration that can be used as part of a comprehensive weight loss program. However, many of these drugs have serious adverse side effects. When less invasive methods have failed, and the patient is at high risk for obesity related morbidity or mortality, weight loss surgery is an option in carefully selected patients with clinically severe obesity. However, these treatments are high-risk, and suitable for use in only a limited number of patients. It is not only obese subjects who wish to lose weight. People with weight within the recommended range, for example, in the upper part of the recommended range, may wish to reduce their weight, to bring it closer to the ideal weight. Thus, a need remains for agents that can be used to effect weight loss in overweight and obese subjects.

SUMMARY

Disclosed herein are findings that peripheral administration of PYY, or an agonist thereof, to a subject results in decreased food intake, caloric intake, and appetite, and an alteration in energy metabolism. The subject can be any subject,

The foregoing and other features and advantages will become more apparent from the following detailed description of several embodiments, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a set of diagrams and digital images showing the generation of transgenic mice expressing EGFP in ARC POMC neurons. Fig. 1a is a schematic diagram of the structure of the POMC-EGFP transgene. Fig. 1b is a digital image showing the identification of a single POMC neuron (arrowhead on recording electrode tip) by EGFP fluorescence (upper) and IR-DIC microscopy (lower) in a living ARC slice prior to electrophysiological recordings. Fig. 1c is a set of digital images showing the co-localization (bright, on right) of EGFP (left) and ß-endorphin immunoreactivity (middle) in ARC POMC neurons. Scale bars: b & c, 50 μm. Fig. 1d is a set of diagrams showing the distribution of EGFP-positive neuronal soma throughout the ARC nucleus. o = 5 cells, • = 10 cells.

Fig. 2 is a tracing and graphs showing activation of MOP-Rs hyperpolarizes the EGFP-labeled POMC neurons by opening G protein-coupled inwardly-rectifying potassium channels. Fig. 2a is a tracing showing met-enkephalin hyperpolarizes POMC neurons and inhibits all action potentials. The horizontal bar indicates the time when 30 μM Met-Enk was bath-applied to the slice. Fig. 2b is a graph showing met-enkephalin current and reversal potential is shifted by extracellular K^+ concentration. Fig. 2c is a graph showing met-enkephalin activates MOP-Rs on POMC neurons. A Met-Enk (30 μM) current was observed and the MOP-R specific antagonist CTAP (1 μM) was applied for 1 minute. Following CTAP Met-Enk elicited no current. The figure is representative of three experiments.

Fig. 3 are tracings and graphs demonstrating that leptin depolarizes POMC neurons via a non-specific cation channel, and decreases GABAergic tone onto POMC cells. Fig. 3a is a tracing demonstrating that leptin depolarizes POMC

intraperitoneal injection of PYY_{3-36}. Freely feeding rats were injected with PYY_{3-36} at the doses indicated (μg/100g), or saline, just prior to 'lights off' and 4-hour cumulative food intake was measured. Results are the mean ± s.e.m. (n = 8 per group), * = $p < 0.05$, ** = $p < 0.01$, *** = < 0.001 compared to saline. Fig. 5b is a bar graph of food intake after intraperitoneal injection of PYY_{3-36}. Fasted rats were injected with PYY_{3-36} at the doses indicated (μg/100g), or saline, and 4-hour cumulative food intake was measured. Results are shown as the mean ± s.e.m. (n = 8 per group), * = $p < 0.05$, ** = $p < 0.01$, *** = < 0.001 compared to saline. Fig. 5c is a bar graph of cumulative food intake after intraperitoneal injection of saline or PYY_{3-36}. Fasted rats were injected with either saline (closed bars) or PYY_{3-36} 5μg/100g (open bars) and cumulative food intake measured at the time points indicated. Results are expressed as mean ± s.e.m. (n = 12 per group), ** = $p < 0.01$ compared to saline. Fig. 5d is a line graph of body weight gain during chronic treatment with PYY_{3-36}. Rats were injected intraperitoneally with PYY_{3-36} 5μg/100g (open squares) or saline (filled inverted triangles) twice daily for 7 days. Body weight gain was calculated each day. Results are expressed as mean ± s.e.m. (n = 12 per group) ** = $p < 0.01$ compared to saline.

Fig. 6 is a set of digital images of c-fos expression in *Pomc-EGFP* mice. Figs. 6a and 6b are digital images of representative sections (bregma –1.4 mm[22]) of c-fos expression in the arcuate nucleus of *Pomc-EGFP* mice response to intraperitoneal saline (Fig. 6a) or PYY_{3-36} (5μg/100g) (Fig. 6b). Scale bar 100 μm. 3V, third ventricle; Arc, arcuate nucleus. Figs. 6c and 6d are digital images of representative sections showing POMC-EGFP neurons (Fig. 6c) and c-fos immunoreactivity (Fig. 6d) either co-localizing (bright arrows) or alone (single darker arrow). Scale bar 25 μm.

Fig. 7 is a set of bar graphs relating to intra-arcuate PYY_{3-36} in rats and feeding effects of IP PYY_{3-36} in *Y2r*- null mice. Fig. 7a is a bar graph of food intake following intra-arcuate PYY_{3-36} injection. Fasted rats were injected with saline or PYY_{3-36} into the arcuate nucleus at the doses indicated. Post-injection 2-hour food intake was measured, ** = $p < 0.01$ compared to saline. Figs. 7b and 7c are bar graphs of feeding response to PYY_{3-36} in *Y2r*-null mice following IP administration:

J. Nutr. 73, 517-30, 1995) show perceived hunger during and after infusions. The results are presented as change from baseline scores and are the mean ± s.e.m. for all 12 subjects.

SEQUENCE LISTING

The nucleic and amino acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases, and three letter code for amino acids, as defined in 37 C.F.R. 1.822. Only one strand of each nucleic acid sequence is shown, but the complementary strand is understood as included by any reference to the displayed strand.

DETAILED DESCRIPTION

I. Abbreviations

α-MSH: alpha melanocortin stimulating hormone

Arc: arcuate nucleus

EPSP: excitatory postsynaptic potential

GABA: γaminobutyric acid

GFP, EGFP: green fluorescent protein

IPSC: inhibitory postsynaptic current

kb: kilobase

kg: kilogram

MOP-R: μ-opiod receptor

MV: millivolts

NPY: neuropeptide Y

pmol: picomole

POMC: proopiomelanocortin

RIA: radioimmunoassay

RPA: RNase protection assay

s.e.m: standard error of the mean

TH: tyrosine hydroxylase

or shape for self-evaluation, and amenorrhea. Associated features often include denial of the illness and resistance to psychotherapy, depressive symptoms, markedly decreased libido, and obsessions or peculiar behavior regarding food, such as hoarding. The disorder is divided into two subtypes, a restricting type, in which weight loss is achieved primarily through diet or exercise, and a binge-eating/purging type, in which binge eating or purging behavior also occur regularly.

Antagonist: A substance that tends to nullify the action of another, as an agent that binds to a cell receptor without eliciting a biological response, blocking binding of substances that could elicit such responses.

Appetite: A natural desire, or longing for food. In one embodiment, appetite is measured by a survey to assess the desire for food. Increased appetite generally leads to increased feeding behavior.

Appetite Suppressants: Compounds that decrease the desire for food. Commercially available appetite suppressants include, but are not limited to, amfepramone (diethylpropion), phentermine, mazindol and phenylpropanolamine fenfluramine, dexfenfluramine, and fluoxetine.

Binding: A specific interaction between two molecules, such that the two molecules interact. Binding can be specific and selective, so that one molecule is bound preferentially when compared to another molecule. In one embodiment, specific binding is identified by a disassociation constant (K_d).

Body Mass Index (BMI): A mathematical formula for measuring body mass, also sometimes called Quetelet's Index. BMI is calculated by dividing weight (in kg) by height^2 (in meters^2). The current standards for both men and women accepted as "normal" are a BMI of 20-24.9 kg/m^2. In one embodiment, a BMI of greater than 25 kg/m^2 can be used to identify an obese subject. Grade I obesity corresponds to a BMI of 25-29.9 kg/m^2. Grade II obesity corresponds to a BMI of 30-40 kg/m^2; and Grade III obesity corresponds to a BMI greater than 40 kg/m^2 (Jequier, *Am. J Clin. Nutr.* 45:1035-47, 1987). Ideal body weight will vary among species and individuals based on height, body build, bone structure, and sex.

c-fos: The cellular homologue of the viral v-fos oncogene found in FBJ (Finkel-Biskis-Jinkins) and FBR murine osteosarcoma viruses (MSV). The human

the temperature of one gram of water at one atmosphere pressure from 0° C to 100° C), food calories are actually equal to 1,000 standard calories (1 food calorie = 1 kilocalorie).

Conservative variation: The replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include the substitution of one hydrophobic residue such as isoleucine, valine, leucine or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acid, or glutamine for asparagine, and the like. The term "conservative variation" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide.

Non-limiting examples of conservative amino acid substitutions include those listed below:

Original Residue	Conservative Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
His	Asn; Gln
Ile	Leu, Val
Leu	Ile; Val
Lys	Arg; Gln; Glu
Met	Leu; Ile
Phe	Met; Leu; Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile; Leu

Depolarization: An increase in the membrane potential of a cell. Certain stimuli reduce the charge across the plasma membrane. These can be electrical stimuli (which open voltage-gated channels), mechanical stimuli (which activate

Hyperpolarization: A decrease in the membrane potential of a cell. Inhibitory neurotransmitters inhibit the transmission of nerve impulses via hyperpolarization. This hyperpolarization is called an inhibitory postsynaptic potential (IPSP). Although the threshold voltage of the cell is unchanged, a hyperpolarized cell requires a stronger excitatory stimulus to reach threshold.

Inhibitory Postsynaptic Current: A current that inhibits an electrophysiological parameter of a postsynaptic cell. The potential of a postsynaptic cell can be analyzed to determine an effect on a presynaptic cell. In one embodiment, the postsynaptic cell is held in voltage clamp mode, and postsynaptic currents are recorded. If necessary, antagonists of other classes of current can be added. In one specific, non-limiting example, to record GABAergic IPSCs, blockers of excitatory channels or receptors can be added. The instantaneous frequency over time is then determined.

In one embodiment, IPSCs give a measure of the frequency of GABA release from an NPY neuron. Thus, as NPY neurons release GABA onto POMC neurons, measurement of IPSC frequency is a gauge of the inhibitory tone that POMC neurons are receiving, and can be used to assess the effect of an agonist of PYY.

Membrane potential: The electrical potential of the interior of the cell with respect to the environment, such as an external bath solution. One of skill in the art can readily assess the membrane potential of a cell, such as by using conventional whole-cell techniques. Activation of a cell is associated with less negative membrane potentials (for example shifts from about –50 mV to about –40 mV). These changes in potential increase the likelihood of action potentials, and thus lead to an increase in the rate of action potentials.

The rate of action potentials can be assessed using many approaches, such as using conventional whole cell access, or using, for example, perforated-patch whole-cell and cell-attached configurations. In each event the absolute voltage or current is not assessed, rather the frequency of rapid deflections characteristic of action potentials is assessed, as a function of time (therefore this frequency is an instantaneous frequency, reported in "bins"). This time component can be related to the time at which a compound, such as a PYY agonist, is applied to the bath to

Dumont et al., *Society for Neuroscience Abstracts* 19:726, 1993). Signal transmission through both the Y1 and the Y2 receptors are coupled to the inhibition of adenylate cyclase. Binding to the Y-2 receptor was also found to reduce the intracellular levels of calcium in the synapse by selective inhibition of N-type calcium channels. In addition, the Y-2 receptor, like the Y1 receptors, exhibits differential coupling to second messengers (see U.S. Patent No. 6,355,478). Y2 receptors are found in a variety of brain regions, including the hippocampus, substantia nigra-lateralis, thalamus, hypothalamus, and brainstem. The human, murine, monkey and rat Y2 receptors have been cloned (e.g., see U.S. Patent No. 6,420,352 and U.S. Patent No. 6,355,478).

A Y2 receptor agonist is a peptide, small molecule, or chemical compound that preferentially binds to the Y2 receptor and stimulates intracellular signaling. In one embodiment, an agonist for the Y2 receptor binds to the receptor with an equal or greater affinity than NPY. In another embodiment, an agonist selectively binds the Y2 receptor, as compared to binding to another receptor.

One of skill in the art can readily determine the dissociation constant (K_d) value of a given compound. This value is dependent on the selectivity of the compound tested. For example, a compound with a K_d which is less than 10 nM is generally considered an excellent drug candidate. However, a compound that has a lower affinity, but is selective for the particular receptor, can also be a good drug candidate. In one specific, non-limiting example, an assay, such as a competition assay, is used to determine if a compound of interest is a Y2 receptor agonist. Assays useful for evaluating neuropeptide Y receptor antagonists are also well known in the art (see U.S. Patent No. 5,284,839, which is herein incorporated by reference, and Walker et al., *Journal of Neurosciences* 8:2438-2446, 1988).

Normal Daily Diet: The average food intake for an individual of a given species. A normal daily diet can be expressed in terms of caloric intake, protein intake, carbohydrate intake, and/or fat intake. A normal daily diet in humans generally comprises the following: about 2,000, about 2,400, or about 2,800 to significantly more calories. In addition, a normal daily diet in humans generally includes about 12 g to about 45 g of protein, about 120 g to about 610 g of carbohydrate, and about 11 g to about 90 g of fat. A low calorie diet would be no

Pancreatic Polypeptide: A 36 amino acid peptide produced by the pancreas that is has homology to PYY and NPY.

Peripheral Administration: Administration outside of the central nervous system. Peripheral administration does not include direct administration to the brain. Peripheral administration includes, but is not limited to intravascular, intramuscular, subcutaneous, inhalation, oral, rectal, transdermal or intra-nasal administration

Polypeptide: A polymer in which the monomers are amino acid residues which are joined together through amide bonds. When the amino acids are alpha-amino acids, either the L-optical isomer or the D-optical isomer can be used, the L-isomers being preferred. The terms "polypeptide" or "protein" as used herein are intended to encompass any amino acid sequence and include modified sequences such as glycoproteins. The term "polypeptide" is specifically intended to cover naturally occurring proteins, as well as those which are recombinantly or synthetically produced. The term "polypeptide fragment" refers to a portion of a polypeptide, for example such a fragment which exhibits at least one useful sequence in binding a receptor. The term "functional fragments of a polypeptide" refers to all fragments of a polypeptide that retain an activity of the polypeptide. Biologically functional peptides can also include fusion proteins, in which the peptide of interest has been fused to another peptide that does not decrease its desired activity.

PYY: A peptide YY polypeptide obtained or derived from any species. Thus, PYY includes the human full length polypeptide (as set forth in SEQ ID NO: 1) and species variations of PYY, including e.g. murine, hamster, chicken, bovine, rat, and dog PYY (SEQ ID NOS: 5-12). In one embodiment, PYY agonists do not include NPY. PYY also includes PYY_{3-36}. A "PYY agonist" is any compound which binds to a receptor that specifically binds PYY, and elicits an effect of PYY. In one embodiment, a PYY agonist is a compound that affects food intake, caloric intake, or appetite, and/or which binds specifically in a Y receptor assay or competes for binding with PYY, such as in a competitive binding assay with labeled PYY. PYY agonists include, but are not limited to, compounds that bind to the Y2 receptor.

Methods for Altering Food Intake, Appetite, Caloric Intake and Energy Expenditure

A method is disclosed herein for reducing food intake by peripherally administering to a subject a therapeutically effective amount of PYY or an agonist of PYY. In one embodiment, administration of PYY, or an agonist of PYY, results in a decrease in the amount, either the total weight or the total volume of food. In other embodiment, administration of PYY, or an agonist thereof, results in a decrease of the intake of a food component, such as a decrease in the ingestion of lipids, carbohydrates, cholesterol, or proteins. In the any of the methods disclosed herein, a preferred compound, PYY $_{3-36}$ can be administered. This disclosure includes the corresponding uses of PYY or an agonist thereof for the manufacture of a medicament for the purposes set herein, and includes the use of PYY_{3-36}.

A method is also disclosed herein for reducing caloric intake by peripherally administering to a subject a therapeutically effective amount of PYY or an agonist of PYY. In one embodiment, total caloric intake is reduced by peripheral administration of a therapeutically effective amount of PYY. In other embodiments, the caloric intake from the ingestion of a specific food component, such as, but not limited to, the ingestion of lipids, carbohydrates, cholesterol, or proteins, is reduced.

In an additional embodiment, a method is disclosed herein for reducing appetite by administering a therapeutically effective amount of PYY or an agonist thereof. Appetite can be measured by any means known to one of skill in the art. For example, decreased appetite can be assessed by a psychological assessment. In this embodiment, administration of PYY results in a change in perceived hunger, satiety, and/or fullness. Hunger can be assessed by any means known to one of skill in the art. In one embodiment, hunger is assessed using psychological assays, such as by an assessment of hunger feelings and sensory perception using a questionnaire, such as, but not limited to, a Visual Analog Score (VAS) questionnaire (see the Examples section). In one specific, non-limiting example, hunger is assessed by answering questions relating to desire for food, drink, prospective food consumption, nausea, and perceptions relating to smell or taste.

In a further embodiment, a method is disclosed herein for altering energy metabolism in a subject. The method includes peripherally administering a

Obesity is currently a poorly treatable, chronic, essentially intractable metabolic disorder. A therapeutic drug useful in weight reduction of obese persons could have a profound beneficial effect on their health. Thus, the subject can be, but is not limited to, a subject who is overweight or obese. In one embodiment, the subject has, or is at risk of having, a disorder wherein obesity or being overweight is a risk factor for the disorder. Disorders of interest include, but are not limited to, cardiovascular disease, (including, but not limited to, hypertension, atherosclerosis, congestive heart failure, and dyslipidemia), stroke, gallbladder disease, osteoarthritis, sleep apnea, reproductive disorders such as, but not limited to, polycystic ovarian syndrome, cancers (e.g., breast, prostate, colon, endometrial, kidney, and esophagus cancer), varicose veins, acnthosis nigricans, eczema, exercise intolerance, insulin resistance, hypertension hypercholesterolemia, cholithiasis, osteoarthritis, orthopedic injury, insulin resistance (such as, but not limited to, type 2 diabetes and syndrome X) and tromboembolic disease (see Kopelman, *Nature* 404:635-43; Rissanen et al., *British Med. J.* 301, 835, 1990).

Other associated disorders also include depression, anxiety, panic attacks, migraine headaches, PMS, chronic pain states, fibromyalgia, insomnia, impulsivity, obsessive compulsive disorder, and myoclonus. Obesity is a recognized risk factor for increased incidence of complications of general anesthesia. (See e. g., Kopelman, *Nature* 404:635-43, 2000). It reduces life span and carries a serious risk of co-morbidities listed above.

Other diseases or disorders associated with obesity are birth defects (maternal obesity associated with increased incidence of neural tube defects), carpal tunnel syndrome (CTS), chronic venous insufficiency (CVI), daytime sleepiness, deep vein thrombosis (DVT), end stage renal disease (ESRD), gout, heat disorders, impaired immune response, impaired respiratory function, infertility, liver disease, lower back pain, obstetric and gynecologic complications, pancreatititis, as well as abdominal hernias, acanthosis nigricans, endocrine abnormalities, chronic hypoxia and hypercapnia, dermatological effects, elephantitis, gastroesophageal reflux, heel spurs, lower extremity edema, mammegaly (causing considerable problems such as bra strap pain, skin damage, cervical pain, chronic odors and infections in the skin folds under the breasts, etc.), large anterior abdominal wall masses (abdominal

promoting appetite; reducing, inhibiting or preventing satiety and sensations of satiety; and increasing, promoting and enhancing hunger and sensations of hunger.

Increased weight gain may be desirable for commercial reasons in animal husbandry. Thus, an antagonist of PYY can be used in humans, companion animals and other objectively or subjectively valuable animals, for example, horses. PYY antagonists can be used to stimulate appetite and increase weight gain when appetite is poor and weight is lost or may be lost. Specific, non-limiting examples include during illness, after accidental or surgical trauma (for example, burns, and especially severe burns), during convalescence, in the elderly, and in anorexia and bulimia, and in other wasting conditions. Appetite stimulation and increase in weight may be particularly desirable in specific conditions, for example, during cachexia (wasting) in AIDS, and in cancer patients.

A suitable administration format may be best determined by the subject or by a medical practitioner. In one embodiment, the pharmaceutical compositions that include PYY, or an agonist thereof, or an antagonist thereof, will preferably be formulated in unit dosage form, suitable for individual administration of precise dosages. An effective amount of PYY or an agonist thereof can be administered in a single dose, or in multiple doses, for example daily, during a course of treatment. In one embodiment, PYY is administered whenever the effect (e.g., appetite suppression, decreased food intake, or decreased caloric intake) is desired. In another embodiment, PYY or an analog thereof is administered slightly prior to whenever the effect is desired, such as, but not limited to about 10 minutes, about 15 minutes, about 30 minutes, about 60 minutes, about 90 minutes, or about 120 minutes, prior to the time the effect is desired. In another embodiment, a time release formulation is utilized.

In one embodiment, a therapeutically effective amount of PYY or an agonist thereof is administered as a single pulse dose, as a bolus dose, or as pulse doses administered over time. Thus, in pulse doses, a bolus administration of PYY is provided, followed by a time period wherein no PYY is administered to the subject, followed by a second bolus administration. In specific, non-limiting examples, pulse doses of PYY are administered during the course of a day, during the course of a week, or during the course of a month.

practitioner for each patient individually. Various pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, e.g., *Remington's Pharmaceutical Sciences* by E. W. Martin. See also Wang, Y. J. and Hanson, M. A., *Journal of Parenteral Science and Technology*, Technical Report No. 10, Supp. 42:2S, 1988.

PYY, PYY agonists, and PYY antagonists useful in the methods of this disclosure can be provided as parenteral compositions, e.g., for injection or infusion. Preferably, they are suspended in an aqueous carrier, for example, in an isotonic buffer solution at a pH of about 3.0 to about 8.0, preferably at a pH of about 3.5 to about 7.4, 3.5 to 6.0, or 3.5 to about 5.0. Useful buffers include sodium citrate-citric acid and sodium phosphate-phosphoric acid, and sodium acetate/acetic acid buffers. A form of repository or "depot" slow release preparation may be used so that therapeutically effective amounts of the preparation are delivered into the bloodstream over many hours or days following transdermal injection or delivery.

Since the PYY and agonists are amphoteric, they may be utilized as free bases, as acid addition salts or as metal salts. The salts must, of course, be pharmaceutically acceptable, and these will include metal salts, particularly alkali and alkaline earth metal salts, e.g., potassium or sodium salts. A wide variety of pharmaceutically acceptable acid addition salts are available. Such products are readily prepared by procedures well known to those skilled in the art.

For use by the physician, the compositions can be provided in dosage unit form containing an amount of a PYY or a PYY agonist with or without another active ingredient, e.g., a food intake-reducing, plasma glucose-lowering or plasma lipid-altering agent. Administration may begin whenever the suppression of nutrient availability, food intake, weight, blood glucose or plasma lipid lowering is desired, for example, at the first sign of symptoms of a weight-related disorder or shortly after diagnosis of obesity, diabetes mellitus, or insulin resistance syndrome.

Therapeutically effective amounts of a PYY or a PYY agonist for use in reducing nutrient availability are those that suppress appetite at a desired level. As will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the potency of the particular compound, age and weight of the patient, the patient's physical condition, the blood sugar level, the

Generally, the formulations are prepared by contacting the PYY, PYY agonist, or PYY antagonist, uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

PPY, PYY antagonists, and PYY agonists are also suitably administered by sustained-release systems. Suitable examples of sustained-release PYY and PYY agonists include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt). Sustained-release PPY, PYY antagonist and PYY agonist compositions may be administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray.

Sustained release matrices include polylactides (U.S. Patent No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers 22*:547-556, 1983, poly(2-hydroxyethyl methacrylate)); (Langer et al., *J. Biomed. Mater. Res.* 15:167-277, 1981; Langer, *Chem. Tech.* 12:98-105, 1982, ethylene vinyl acetate (Langer et al., *Id.*) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release PPY, PYY antagonists and PYY agonists include liposomally PPY and PYY agonists (see generally, Langer, *Science* 249:1527-1533, 1990; Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317-327 and 353-365, 1989). Liposomes containing PPY peptide and peptide analogs are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. U.S.A.* 82:3688-3692, 1985; Hwang et al., *Proc. Natl. Acad. Sci. U.S.A.* 77:4030-4034, 1980; EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Patent

programmable pump. Such pumps typically include a drug reservoir, a peristaltic pump to pump out the drug from the reservoir, and a catheter port to transport the pumped out drug from the reservoir via the pump to a patient's anatomy. Such devices also typically include a battery to power the pump as well as an electronic module to control the flow rate of the pump. The Medtronic SynchroMed™ pump further includes an antenna to permit the remote programming of the pump. Passive drug infusion devices, in contrast, do not feature a pump, but rather rely upon a pressurized drug reservoir to deliver the drug. Thus such devices tend to be both smaller as well as cheaper as compared to active devices. An example of such a device includes the Medtronic IsoMed™. This device delivers the drug into the patient through the force provided by a pressurized reservoir applied across a flow control unit.

The implanted pump can be completely implanted under the skin of a patient, thereby negating the need for a percutaneous catheter. These implanted pumps can provide the patient with PYY, PYY antagonist, or a PYY agonist at a constant or a programmed delivery rate, e.g., to give pulsed doses at or around meal time. Constant rate or programmable rate pumps are based on either phase-change or peristaltic technology. When a constant, unchanging delivery rate is required, a constant-rate pump is well suited for long-term implanted drug delivery. If changes to the infusion rate are expected, a programmable pump may be used in place of the constant rate pump system. Osmotic pumps may be much smaller than other constant rate or programmable pumps, because their infusion rate can be very low. An example of such a pump is described listed in U.S. Patent No. 5,728,396.

For oral administration, the pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets can be coated by methods well known in the art. Liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions,

formulations usually comprise injectable fluids that are pharmaceutically and physiologically acceptable fluid vehicles such as water, physiological saline, other balanced salt solutions, aqueous dextrose, glycerol or the like. Excipients that can be included are, for instance, other proteins, such as human serum albumin or plasma preparations. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate. Other medicinal and pharmaceutical agents, for instance other appetite suppressants, or protease inhibitors, also may be included. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in the art.

The dosage form of the pharmaceutical composition will be determined by the mode of administration chosen. For instance, in addition to injectable fluids, inhalation, suppository, and oral formulations can be employed. The pharmaceutical compositions can be produced of conventional mixing, granulating, confectioning, dissolving or lyophilizing processes.

Oral formulations may be liquid (e.g., syrups, solutions or suspensions), or solid (e.g., powders, pills, tablets, or capsules). For example, pharmaceutical compositions for oral use can be obtained by combining the active ingredient with one or more solid carriers, optionally granulating a resulting mixture, and, if desired, processing the mixture or granules, if appropriate with the addition of additional excipients, to form tablets or dragee cores.

Suitable carriers include fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyffolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients include flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts

In one embodiment, a therapeutically effective amount of PYY or an agonist thereof is administered with a therapeutically effective amount of another agent, such as, but not limited to, an additional appetite suppressant. Specific, non-limiting example of an additional appetite suppressant include amfepramone (diethylpropion), phentermine, mazindol and phenylpropanolamine, fenfluramine, dexfenfluramine, and fluoxetine. PYY and/or a PYY agonist can be administered simultaneously with the additional appetite suppressant, or they may be administered sequentially. Thus, in one embodiment, PYY is formulated and administered with an appetite suppressant as a single dose.

Additionally, a method of treating obesity is disclosed herein. The method includes administering to an obese subject a therapeutically effective amount of PYY or a PYY agonist. The PYY agonist can have potency in at least one of food intake or gastric emptying greater than NPY. PYY and/or the PYY agonist can be administered peripherally, such as in a single or divided dose. Suitable single or divided doses include, but are not limited to, 1 μg to about 5 mg or about 0.01 μg/kg to about 500 μg/kg per dose. The subject can be insulin resistant or glucose intolerant, or both. In addition to being obese, the subject can have diabetes mellitus.

A method of reducing food intake is also disclosed herein. The method includes administering to an obese subject a therapeutically effective amount of PYY or a PYY agonist. The PYY agonist can have potency in at least one of food intake or gastric emptying greater than NPY. PYY and/or the PYY agonist can be administered peripherally, such as in a single or divided dose. Suitable single or divided doses include, but are not limited to, 1 μg to about 5 mg or about 0.01 μg/kg to about 500 μg/kg per dose. The subject can have Type II diabetes, and/or can be overweight.

A method is disclosed herein for improving lipid profile in a subject. The method includes administering to the subject an effective amount of PYY or a PYY agonist. An improvement in lipid profile includes, but is not limited to, at least one of reducing cholesterol levels, reducing triglyceride levels and increasing HDL cholesterol levels. PYY and/or the PYY agonist can be administered peripherally, such as in a single or divided dose. PYY and/or the PYY agonist can be

exert an effect at supraphysiological levels when administered peripherally, and side-effects are observed. No side effects are observed when PYY $_{3-36}$ is used. Without being bound by theory, PYY_{3-36} does not affect Y2 receptors throughout the brain, which could cause side effects. It should be noted, without being limiting, that a further advantage of PYY_{3-36} is that PYY_{3-36} does not increase blood pressure. The effects of PYY_{3-36} are as long lasting as 24 hours. Recipients claim a decrease in appetite over that period, and a reduction of food intake of about one third has been reported.

In one specific, non-limiting example, PYY_{3-36} is administered in a dose of about 1 nmol or more, 2 nmol or more, or 5 nmol or more. In this example, the dose of PYY_{3-36} is generally not more than 100 nmol, for example, the dose is 90 nmols or less, 80 nmols or less, 70 nmols or less, 60 nmols or less, 50 nmols or less, 40 nmols or less, 30 nmols or less, 20 nmols or less, 10 nmols. For example, a dosage range may comprise any combination of any of the specified lower dose limits with any of the specified upper dose limits. Thus, exemplar non-limiting dose ranges include a dose of PYY_{3-36} may be within the range of form 1 to 100 n mols, from 1 to 90 mols, from 1 to 80 nmols. Exemplary, non-limiting dose ranges include, from 2 to 100 nmols, from 2 to 90 n mols, for example, from 2 to 80 nmols etc., from 5 nmols to 100 mols, from 5 nmols to 90 nmols, from 5 nmols to 80 nmols etc. By way of example, a dose of from about 5 to about 50 nmol may be administered such as, but not limited to, from about 2 to about 20 nmol, for example, about 10 nmol. The selected dose may be administered for example, by injection, for example, as a subcutaneous injection. In one embodiment, a dose of PYY or PYY_{3-36} at 0.143 n moles ($1/7^{th}$ of a mole) is administered per kilogram, to achieve a dose that is similar to the postparandial level of PYY.

If PYY or an agonist thereof is used, the dose is preferably a molar equivalent of a PYY_{3-36} dose, as described above. The doses can be calculated on the basis of a subject, such as a subject weighing from 70 to 75 kg. The exact dose is readily determined by one of skill in the art based on the potency of the specific compound (such as the PYY polypeptide, or agonist) utilized, and the age, weight, sex and physiological condition of the subject.

available molecules. In addition, other brain sites that express the Y2 receptor are protected by the blood/brain barrier. Without being bound by theory, agents able to bind to the arcuate Y2R, but that do not cross the blood/brain barrier following peripheral administration, are likely to be of use.

In one embodiment, a PYY agonist is a compound that affects food intake, caloric intake, or appetite, and/or which binds specifically in a Y receptor assay or competes for binding with PYY, such as in a competitive binding assay with labeled PYY. PYY agonists include, but are not limited to, compounds that bind to the Y2 receptor.

PYY and agonists useful in the methods disclosed herein include, but are not limited to, polypeptides comprising, or alternatively consisting of, the amino acid sequence for PPY and agonists thereof, e.g., mutants, fragments and/or variants thereof. Variants include deletions, insertions, inversions, repeats and substitutions (e.g., conservative substitutions and non-conservative substitutions; see, e.g., Tables 1 and 2, *infra*). More than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) can be deleted or inserted or substituted with another amino acid. Typically conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of Ser and Thr containing hydroxy residues, interchange of the acidic residues Asp and Glu, interchange between the amide residues Asn and Gln, interchange of the basic residues Lys and Arg, interchange of the aromatic residues Phe and Tyr, and interchange of the small-sized amino acids Ala, Ser, Thr, Met and Gly. Guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., *Science* 247:1306-1310, 1990.

As another example, polypeptide fragments may contain a continuous series of deleted residues from the amino (N)- or the carboxyl (C)- terminus, or both (see, e.g., Tables 1 and 2, *infra*). Any number of amino acids, ranging from 1 to 24, can be deleted from the N-terminus, the C-terminus or both.

Furthermore, the agonist polypeptides may also include, but are not limited to, polypeptides comprising, or alternatively consisting of, internal deletions of the amino acid sequences for PPY and/or agonist thereof (see, e.g., Table 2, *infra*). Such deletions may comprise one or more amino acid residue deletions (e.g., one,

peptide, or vice versa. Optionally, a cleavable linker region may be used linking the PYY or PYY agonist to the fusion partner, and may be cleaved *in vivo* thereby resulting in the release of an active form of PYY or a PYY agonist. Examples of such cleavage regions include, but are not limited to, the linker regions D-D-D-D-Y (SEQ ID NO: 330), G-P-R (SEQ ID NO: 331), A-G-G (SEQ ID NO: 332) and H-P-F-H-L (SEQ ID NO 333), which can be cleaved by enterokinase, thrombin, ubiquitin cleaving enzyme and renin, respectfully. See, e.g., U.S. Patent No. 6,410,707.

Also contemplated as useful PYY agonists are Y2 specific NPY peptide agonists as described in U.S. Patent No. 5,026,685; U.S. Patent No. 5,574,010; U.S. Patent No. 5,604,203; U.S. Patent No. 5,696,093; U.S. Patent No. 6,046,167. See below:

Preferred PPY agonists are described herein as follows.

TABLE 1 - PYY: Variation Among Species

PEPTIDE YY	AA SEQUENCE
Human	YPIKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 1)
Rat	YPAKPEAPGEDASPEELSRYYASLRHYLNLVTRQRY (SEQ ID NO: 5)
Pig	YPAKPEAPGEDASPEELSRYYASLRHYLNLVTRQRY (SEQ ID NO: 6)
Guinea pig	YPSKPEAPGSDASPEELARYYASLRHYLNLVTRQRY (SEQ ID NO: 7)
Frog	YPPKPENPGEDASPEEMTKYLTALRHYINLVTRQRY (SEQ ID NO: 8)
Raja	YPPKPENPGDDAAPEELAKYYSALRHYINLITRQRY (SEQ ID NO: 9)
Dogfish	YPPKPENPGEDAPPEELAKYYSALRHYINLITRQRY (SEQ ID NO: 10)
Lampetra	FPPKPDNPGDNASPEQMARYKAAVRHYINLITRQRY (SEQ ID NO: 11)
Petromyzon	MPPKPDNPSPDASPEELSKYMLAVRNYINLITRQRY (SEQ ID NO: 12)

NEUROPEPTIDE Y	AA SEQUENCE
Human	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 2)
Rat	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 13)
Rabbit	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 14)
Dog	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 15)
Pig	YPSKPDNPGEDAPAEDLARYYSALRHYINLITRQRY (SEQ ID NO: 16)
Cow	YPSKPDNPGEDAPAEDLARYYSALRHYINLITRQRY (SEQ ID NO: 17)
Sheep	YPSKPDNPGDDAPAEDLARYYSALRHYINLITRQRY (SEQ ID NO: 18)

Ref: See, e.g., Balasubramaniam et al., *Pept Res* 1(1):32-5, Sep-Oct 1998; Liu et al., *J Gastrointest Surg* 5(2):147-52, Mar-Apr 2001.

PEPTIDE SEQUENCE

NPY (human)

YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 2)

Ref: Tatemoto et al., *Proc Natl Acad Sci* U.S.A. 79:5485-9, 1982.

Variations of NPY

N-Terminal Deletions of NPY, including but not limited to: NPY(26-36), NPY(25-36), NPY(24-36), NPY(23-36), NPY(22-36), NPY(21-36), NPY(20-36), NPY(19-36), NPY(18-36), NPY(17-36), NPY(16-36), NPY(15-36), NPY(14-36), NPY(13-36), NPY(12-36), NPY(11-36), NPY(10-36), NPY(9-36), NPY(8-36), NPY(7-36), NPY(6-36), NPY(5-36), NPY(4-36), NPY(3-36).

Ref: See e.g., Gehlert et al., *Proc Soc Exp Biol Med* 218:7-22, 1998; Sheikh et al., *Am J Physiol* 261:G701-15, Nov. 1991.

Internal Deletions, including but not limited to: (1-4)-Aca-(14-36)pNPY, (1-4)-Aca-(15-36)pNPY, (1-4)-Aca-(16-36)pNPY, (1-4)-Aca-(17-36)pNPY, (1-4)-Aca-(18-36)pNPY, (1-4)-(31-36)pNPY11, (1-4)-Aca-(31-36)pNPY, (4-1)-(31-36)pNPY, (4-1)-Aca-(31-36)pNPY, $(4\text{-}1)_D$-(31-36)pNPY, $(4\text{-}1)_D$-Aca-(31-36)pNPY.

Ref: Fournier et al., *Mol Pharmacol* 45(1):93-101, Jan 1994.

Additional Internal Deletion Mutants, including but not limited to: des-$AA^{10\text{-}17}$-NPY, des-$AA^{10\text{-}17}$, Ac-[D-Lys^9(ε-Ac-Ala)]NPY, des-$AA^{10\text{-}17}$, Ac[D-Lys^9(ε-Ac-Ala)]NPY, des-$AA^{10\text{-}17}$[$Ala^{7,21}$]NPY, des-$AA^{10\text{-}17}$[$Cys^{7,21}$]NPY, des-$AA^{10\text{-}17}$[Glu^7,Lys^{21}]NPY, des-$AA^{11\text{-}17}$[D-Lys^{10}(ε-Ac), $Cys^{7,21}$]NPY, des-$AA^{10\text{-}17}$[D-Cys^7, D-Lys(ε-Ac), Cys^{21}]NPY,des-$AA^{10\text{-}17}$[D-Cys^7, Lys^9(ε-Ac), Cys^{21}]NPY, des-$AA^{10\text{-}17}$[$Cys^{7,21}$, Pro^{34}]NPY, des-$AA^{10\text{-}17}$[Asp^7, Dpr^{21}, Pro^{34}]NPY, des-$AA^{10\text{-}17}$[Glu^7, Lys^{21}, Pro^{34}]NPY, des-$AA^{10\text{-}17}$[$Cys^{7,21}$, Leu^{31}, Pro^{34}]NPY, des-$AA^{10\text{-}20}$[$Cys^{7,21}$, Pro^{34}]NPY, des-$AA^{10\text{-}17}$[$Cys^{2,27}$]NPY, des-$AA^{10\text{-}17}$[Cys^2, D-Cys^{27}]NPY.

Ref: Kirby et al., *J Med Chem* 38:4579-86, 1995.

Ref: Potter et al., *Eur J Pharmacol* 267(3):253-262, May 17, 1994.

PEPTIDE SEQUENCE

N-Acetyl [Leu^{28}, Leu^{31}] NPY(24-36)

LRHYLNLLTRQRY (SEQ ID NO: 214)

Ref: Potter et al., *Eur J Pharmacol* 267(3):253-262, May 17, 1994.

PEPTIDE SEQUENCE

[Leu^{28}, Leu^{31}] NPY(24-36)

LRHYLNLLTRQRY (SEQ ID NO: 215)

Ref: Potter et al., *Eur J Pharmacol* 267(3):253-262, May 17, 1994.

PEPTIDE SEQUENCE

[Leu^{17}, Gln^{19}, Ala^{21}, Ala^{22}, Glu^{23}, Leu^{28}, Leu^{31}] NPY(13-36)

PAEDLAQYAAELRHYLNLLTRQRY (SEQ ID NO: 216)

Ref: Potter et al., Eur J Pharmacol 267(3):253-262, May 17, 1994.

PEPTIDE SEQUENCE

Cyclo S-S [Cys^{20},Cys^{24}]pNPY

SKPDNPGEDAPAEDMARCYSACRHYINLITRQRY (SEQ ID NO: 315)

Ref: Soll et al., *Eur J Biochem* 268(10):2828-37, May 2001.

PEPTIDE SEQUENCE

Cyclo-(28/32)-Ac-[Lys^{28}-Glu^{32}]-(25-36)-pNPY

RHYLNLIGRQRY (SEQ ID NO: 316)

Ref: Cabrele et al., *J Pept Sci* 6(3):97-122, Mar 2000.

PEPTIDE SEQUENCE

Cyclo-(27/31)-Ac-[Glu^{27}-Lys^{31}]-(25-36)-pNPY

RHGLNLLGRQRY (SEQ ID NO: 317)

Ref: Cabrele et al., *J Pept Sci* 6(3):97-122, Mar 2000.

PEPTIDE SEQUENCE

[Tyr^{32}, Leu^{34}]NPY(27-36)

YINLIYRLRY (SEQ ID NO: 318)

Ref: Leban et al., *J Med Chem* 38:1150-57, 1995.

TABLE 3 – EXAMPLES OF CONSERVATIVE AMINO ACID SUBSTITUTIONS OF PYY

Single point mutations of PYY(25-36)

PEPTIDE	SEQUENCE
[Lys^{25}]PPY(25-36)	KHYLNLVTRQRY (SEQ ID NO: 36)
[Thr^{27}]PPY(25-36)	RHTLNLVTRQRY (SEQ ID NO: 37)
[Phe^{27}]PPY(25-36)	RHFLNLVTRQRY (SEQ ID NO: 38)
[Ile^{28}]PYY (25-36)	RHYINLVTRQRY (SEQ ID NO: 39)
[Val^{28}]PYY (25-36)	RHYVNLVTRQRY (SEQ ID NO: 40)
[Gln^{29}]PYY (25-36)	RHYLQLVTRQRY (SEQ ID NO: 41)
[Ile^{30}]PYY (25-36)	RHYLNIVTRQRY (SEQ ID NO: 42)
[Val^{30}]PYY (25-36)	RHYLNVVTRQRY (SEQ ID NO: 43)
[Ile^{31}]PYY (25-36)	RHYLNLITRQRY (SEQ ID NO: 44)
[Leu^{31}]PYY (25-36)	RHYLNLLTRQRY (SEQ ID NO: 45)
[Ser^{32}]PYY (25-36)	RHYLNLVSRQRY (SEQ ID NO: 46)
[Lys^{33}]PYY (25-36)	RHYLNLVTKQRY (SEQ ID NO: 47)
[Asn^{34}]PYY (25-36)	RHYLNLVTRNRY (SEQ ID NO: 48)
[Lys^{35}]PYY (25-36)	RHYLNLVTRQKY (SEQ ID NO: 49)
[Thr^{36}]PYY (25-36)	RHYLNLVTRQRT (SEQ ID NO: 50)
[Phe^{36}]PYY (25-36)	RHYLNLVTRQRF (SEQ ID NO: 51)

Double point mutations

PEPTIDE	SEQUENCE
[Lys^{25}, Thr^{27}]PPY(25-36)	KHTLNLVTRQRY (SEQ ID NO: 52)
[Lys^{25}, Phe^{27}]PPY(25-36)	KHFLNLVTRQRY (SEQ ID NO: 53)
[Lys^{25}, Ile^{28}]PPY(25-36)	KHYINLVTRQRY (SEQ ID NO: 54)
[Lys^{25}, Val^{28}]PPY(25-36)	KHYVNLVTRQRY (SEQ ID NO: 55)
[Lys^{25}, Gln^{29}]PPY(25-36)	KHYLQLVTRQRY (SEQ ID NO: 56)
[Lys^{25}, Ile^{30}]PPY(25-36)	KHYLNIVTRQRY (SEQ ID NO: 57)
[Lys^{25}, Val^{30}]PPY(25-36)	KHYLNVVTRQRY (SEQ ID NO: 58)
[Lys^{25}, Ile^{31}]PPY(25-36)	KHYLNLITRQRY (SEQ ID NO: 59)
[Lys^{25}, Leu^{31}]PPY(25-36)	KHYLNLLTRQRY (SEQ ID NO: 60)
[Lys ^{25}, Ser ^{32}]PPY(25-36)	KHYLNLVSRQRY (SEQ ID NO: 61)
[Lys^{25}, Lys^{33}]PPY(25-36)	KHYLNLVTKQRY (SEQ ID NO: 62)
[Lys^{25}, Asn^{34}]PPY(25-36)	KHYLNLVTRNRY (SEQ ID NO: 63)

[Ile^{30}, Ile^{31}]PYY (25-36)	RHYLNIITRQRY (SEQ ID NO: 103)
[Ile^{30}, Leu^{31}]PYY (25-36)	RHYLNILTRQRY (SEQ ID NO: 104)
[Ile^{30}, Ser^{32}]PYY (25-36)	RHYLNIVSRQRY (SEQ ID NO: 105)
[Ile^{30}, Lys^{33}]PYY (25-36)	RHYLNIVTKQRY (SEQ ID NO: 106)
[Ile^{30}, Asn^{34}]PYY (25-36)	RHYLNIVTRNRY (SEQ ID NO: 107)
[Ile^{30}, Lys^{35}]PYY (25-36)	RHYLNIVTRQKY (SEQ ID NO: 108)
[Ile^{30}, Thr^{36}]PYY (25-36)	RHYLNIVTRQRT (SEQ ID NO: 109)
[Ile^{30}, Phe^{36}]PYY (25-36)	RHYLNIVTRQRF (SEQ ID NO: 110)
[Val^{30}, Ile^{31}]PYY (25-36)	RHYLNVITRQRY (SEQ ID NO: 111)
[Val^{30}, Leu^{31}]PYY (25-36)	RHYLNVLTRQRY (SEQ ID NO: 112)
[Val^{30}, Ser^{32}]PYY (25-36)	RHYLNVVSRQRY (SEQ ID NO: 113)
[Val^{30}, Lys^{33}]PYY (25-36)	RHYLNVVTKQRY (SEQ ID NO: 114)
[Val^{30}, Asn^{34}]PYY (25-36)	RHYLNVVTRNRY (SEQ ID NO: 115)
[Val^{30}, Lys^{35}]PYY (25-36)	RHYLNVVTRQKY (SEQ ID NO: 116)
[Val^{30}, Thr^{36}]PYY (25-36)	RHYLNVVTRQRT (SEQ ID NO: 117)
[Val^{30}, Phe^{36}]PYY (25-36)	RHYLNVVTRQRF (SEQ ID NO: 118)
[Ile^{31}, Ser^{32}]PYY (25-36)	RHYLNLISRQRY (SEQ ID NO: 119)
[Ile^{31}, Lys^{33}]PYY (25-36)	RHYLNLITKQRY (SEQ ID NO: 120)
[Ile^{31}, Asn^{34}]PYY (25-36)	RHYLNLITRNRY (SEQ ID NO: 121)
[Ile^{31}, Lys^{35}]PYY (25-36)	RHYLNLITRQKY (SEQ ID NO: 122)
[Ile^{31}, Thr^{36}]PYY (25-36)	RHYLNLITRQRT (SEQ ID NO: 123)
[Leu^{31}, Phe^{36}]PYY (25-36)	RHYLNLITRQRF (SEQ ID NO: 124)
[Leu^{31}, Ser^{32}]PYY (25-36)	RHYLNLLSRQRY (SEQ ID NO: 125)
[Val^{31}, Lys^{33}]PYY (25-36)	RHYLNLLTKQRY (SEQ ID NO: 126)
[Leu^{31}, Asn^{34}]PYY (25-36)	RHYLNLLTRNRY (SEQ ID NO: 127)
[Leu^{31}, Lys^{35}]PYY (25-36)	RHYLNLLTRQKY (SEQ ID NO: 128)
[Leu^{31}, Thr^{36}]PYY (25-36)	RHYLNLLTRQRT (SEQ ID NO: 129)
[Leu^{31}, Phe^{36}]PYY (25-36)	RHYLNLLTRQRF (SEQ ID NO: 130)
[Ser^{32}, Lys^{33}]PYY (25-36)	RHYLNLVSKQRY (SEQ ID NO: 131)
[Ser^{32}, Asn^{34}]PYY (25-36)	RHYLNLVSRNRY (SEQ ID NO: 132)
[Ser^{32}, Lys^{35}]PYY (25-36)	RHYLNLVSRQKY (SEQ ID NO: 133)
[Ser^{32}, Thr^{36}]PYY (25-36)	RHYLNLVSRQRT (SEQ ID NO: 134)
[Ser^{32}, Phe^{36}]PYY (25-36)	RHYLNLVSRQRY (SEQ ID NO: 135)
[Lys^{33}, Asn^{34}]PYY (25-36)	RHYLNLVTKNRY (SEQ ID NO: 136)
[Lys^{33}, Lys^{35}]PYY (25-36)	RHYLNLVTKQKY (SEQ ID NO: 137)
[Lys^{33}, Thr^{36}]PYY (25-36)	RHYLNLVTKQRT (SEQ ID NO: 138)
[Lys^{33}, Phe^{36}]PYY (25-36)	RHYLNLVTKQRF (SEQ ID NO: 139)
[Asn^{34}, Lys^{35}]PYY (25-36)	RHYLNLVTRNKY (SEQ ID NO: 140)
[Asn^{34}, Thr^{36}]PYY (25-36)	RHYLNLVTRNRT (SEQ ID NO: 141)

mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(23-36), e.g., [Lys^{25}]PPY(22-36) (Amino acid sequence=ASLKHYLNLVTRQRY (SEQ ID NO: 193)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 150.

Point Mutations of PYY(21-36)

PEPTIDE	SEQUENCE
PYY(21-36)	YASLRHYLNLVTRQRY (SEQ ID NO: 152)
[Thr^{21}]PYY(21-36)	TASLRHYLNLVTRQRY (SEQ ID NO: 153)
[Phe^{21}]PYY(21-36)	FASLRHYLNLVTRQRY (SEQ ID NO: 154)

Also included as PYY(21-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these three mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(22-36), e.g., [Lys^{25}]PPY(21-36) (Amino acid sequence=YASLKHYLNLVTRQRY (SEQ ID NO: 194)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 152.

Point Mutations of PYY(20-36)

PEPTIDE	SEQUENCE
PYY(20-36)	YYASLRHYLNLVTRQRY (SEQ ID NO: 155)
[Thr^{20}]PYY(20-36)	TYASLRHYLNLVTRQRY (SEQ ID NO: 156)
[Phe^{20}]PYY(20-36)	FYASLRHYLNLVTRQRY (SEQ ID NO: 157)

Also included as PYY(20-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these three mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(21-36), e.g., [Lys^{25}]PPY(20-36) (Amino acid sequence=YYASLKHYLNLVTRQRY (SEQ ID NO: 195)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 155.

Point Mutations of PYY(19-36)

PEPTIDE	SEQUENCE
PYY(19-36)	RYYASLRHYLNLVTRQRY (SEQ ID NO: 158)

Point Mutations of PYY(16-36)

PEPTIDE	SEQUENCE
PYY(16-36)	ELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 165)
[Asp^{16}]PYY(16-36)	DLNRYYASLRHYLNLVTRQRY (SEQ ID NO: 166)

Also included as PYY(16-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(17-36), e.g., [Lys^{25}]PPY(16-36) (Amino acid sequence=ELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 199)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 165.

Point Mutations of PYY(15-36)

PEPTIDE	SEQUENCE
PYY(15-36)	EELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 167)
[Asp^{15}]PYY(15-36)	DELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 168)

Also included as PYY(15-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(16-36), e.g., [Lys^{25}]PPY(15-36) (Amino acid sequence=EELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 200)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 167.

Point Mutations of PYY(14-36)

PEPTIDE	SEQUENCE
PYY(14-36)	PEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 169)

Also included as PYY(14-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of this PYY(14-36) mutant with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(15-36), e.g., [Lys^{25}]PPY(23-36) (Amino acid

mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(12-36), e.g., [Lys^{25}]PPY(11-36) (Amino acid sequence=DASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 204)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 174.

Point Mutations of PYY(10-36)

PEPTIDE	SEQUENCE
PYY(10-36)	EDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 176)
[Asp^{10}]PYY(10-36)	DDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 177)

Also included as PYY(10-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(11-36), e.g., [Lys^{25}]PPY(10-36) (Amino acid sequence=EDASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 205)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 176.

Point Mutations of PYY(9-36)

PEPTIDE	SEQUENCE
PYY(9-36)	GEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 178)

Also included as PYY(9-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of this PPY(9-36) mutant with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(10-36), e.g., [Lys^{25}]PPY(9-36) (Amino acid sequence=GEDASPEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 206)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 178.

Potin Mutations of PYY(8-36)

PEPTIDE	SEQUENCE
PYY(8-36)	PGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 179)

Point Mutations of PYY(5-36)

PEPTIDE	SEQUENCE
PYY(5-36)	PEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 184)

Also included as PYY(5-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of this PPY(5-36) mutant with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(6-36), e.g., [Lys^{25}]PPY(5-36) (Amino acid sequence=PEAPGEDASPEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 210)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 184.

Point Mutations of PYY(4-36)

PEPTIDE	SEQUENCE
PYY(4-26)	KPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 185)
[Arg^4]PYY(4-36)	RPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 186)
[Gln^4]PYY(4-36)	QPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 187)
[Asn^4]PYY(4-36)	NPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 188)

Also included as PYY(4-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these four mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(5-36), e.g., [Lys^{25}]PPY(4-36) (Amino acid sequence=KPEAPGEDASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 211)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 185.

Point Mutations of PYY(3-36)

PEPTIDE	SEQUENCE
PYY(3-36)	IKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 1)
[Leu^3]PYY(3-36)	LKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 189)
[Val^3] PYY(3-36)	VKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 190)

Other contemplated NPY analogs have the formula:

X-R_{17} -R_{18} -Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-R_{27}-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-R_{36}-NH_2,

wherein R_{17} is Arg or Leu and R_{18} is Ser or Ala or Ile; and wherein X, R_{27} and R_{36} are as previously indicated.

Still other preferred NPY analogs have the formula:

X-R_{18}-Arg-Tyr-Tyr-Ala-Ser-Leu-R_{25}-His-R_{27}-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-R_{36}-NH_2,

wherein X is desamino or C^a Me or N^a Me and wherein R_{18}, R_{25}, R_{27} and R_{36} are as previously indicated.

Examples of such NPY agonists include:

pNPY (17-36) having the formula:
H-Leu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 217)

The peptide hNPY (17-36) having the formula:
H-Met-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 218)

The peptide [Phe^{27}]-NPY (18-36) having the formula:
H-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 219)

The peptide [Ac-D-Ala^{17}]-NPY (17-36) having the formula:

H-Ala-Arg-Phe-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 228)

The peptide [C^a $MeLeu^{17}$]-pNPY (17-36) having the formula:
H-C^a MeLeu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 229)

The peptide [N^a $MeLeu^{17}$]-pNPY (17-36) having the formula:
H-N^a MeLeu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln- Arg-Tyr-NH_2 (SEQ ID NO: 230)

The peptide [desamino Ala^{18}]-NpY (18-36) having the formula:
desamino-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr- NH_2 (SEQ ID NO: 231)

The peptide [For-Ala^{18}, Glu^{23}, Arg^{26}]-NPY (18-36) having the formula:
For-Ala-Arg-Tyr-Tyr-Ser-Glu-Leu-Arg-Arg-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 232)

The peptide [Nva^{17}, Ala^{21}, Leu^{28}]-NPY (17-36) having the formula:
H-Nva-Ala-Arg-Tyr-Ala-Ser-Ala-Leu-Arg-His-Tyr-Leu-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 233)

The peptide [Thr^{22}, Gln^{23}]-NPY (18-36) having the formula:
H-Ala-Arg-Tyr-Tyr-Thr-Gln-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 234)

The peptide [desamino Leu^{17}, Asn^{23}, Val^{30}]-NPY (17-36) having the formula:
H-desamino Leu-Ala-Arg-Tyr-Tyr-Ser-Asn-Leu-Arg-His-Tyr-Ile-Asn-Val-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 235)

The peptide [Bz-Leu^{17}, Pro^{34}, Phe^{36}]-pNPY (17-36) having the formula: Bz-Leu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Pro-Arg-Phe-NH_2 (SEQ ID NO: 244)

The peptide [Lys^{19}, Phe^{27}, Val^{28}]-NpY (18-36) having the formula: H-Ala-Lys-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Phe-Val-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 245)

The peptide [D-Ala^{17}, Val^{28}, Phe^{32}]-NPY (17-36) having the formula: D-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Val-Asn-Leu-Ile-Phe-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 246)

The peptide [C^{a} MeSer^{18}, Met^{30}, Phe^{36}]-NPY (18-36) having the formula: H-C^{a} MeSer-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Met-Ile-Thr-Arg-Gln-Arg-Phe-NH_2 (SEQ ID NO: 247)

The peptide [Arg^{17}, Ile^{18}, Phe^{27,36}]-NPY (17-36) having the formula: H-Arg-Ile-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Phe-NH_2 (SEQ ID NO: 248)

The peptide [Ser^{18}, Phe^{27}]-pNPY (17-36) having the formula: H-Leu-Ser-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 249)

The peptide [N^{a} MeIle^{18}, Gln^{25}, Phe^{27}]-NPY (18-36) having the formula: N^{a} MeIle-Arg-Tyr-Tyr-Ser-Ala-Leu-Gln-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 250)

The peptide [D-Ser^{18}, Phe^{36}]-NPY (18-36) having the formula: H-D-Ser-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Phe-NH_2 (SEQ ID NO: 251)

A^{26} is His, Thr, 3-Me-His, 1-Me-His, β-pyrozolylalanine, N-Me-His, Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1 -C_{10} alkyl group, or an aryl group), Orn, or is deleted;

A^{27} is an aromatic amino acid other than Tyr;

A^{28} is Leu, Ile, Vat, Trp, Aib, Aib, Anb, or N-Me-Leu;

A^{29} is Asn, Ala, Gln, Gly, Trp, or N-Me-Asn;

A^{30} is Leu, Ile, Val, Trp, Aib, Anb, or N-Me-Leu;

A^{31} is Vat, Ile, Trp, Aib, Anb, or N-Me-Val;

A^{32} is Thr, Ser, N-Me-Set, or N-Me-Thr;

R_3 is H, C_1 -C_{12} alkyl (e.g., methyl), C_6 -C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1 -C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7 -C_{18} aralkyl (e.g., benzyl), or C_7 -C_{18} alkaryl (e.g., p-methylphenyl);

R_4 is H, C_1 -C_{12} alkyl (e.g., methyl), C_6 -C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1 -C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7 -C_{18} aralkyl (e.g., benzyl), or C_7 -C_{18} alkaryl (e.g., p-methylphenyl), or a pharmaceutically acceptable salt thereof. See U.S. Patent No. 5,574,010.

Particularly preferred agonists of this formula to be used in the method of the disclosure include:

N-α-Ala-Ser-Leu-Arg-His-Trp-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 255).

Other peptide YY agonists have the formula:

$$R_2\text{-}A^{25}\text{-}A^{26}\text{-}A^{27}\text{-}A^{28}\text{-}A^{29}\text{-}A^{30}\text{-}A^{31}\text{-}A^{32}\text{-}Y\text{-}R_4$$

(R_1 and R_3 are attached to the N-terminal amino acid)

wherein:

the N-terminal amino acid bonds to R_1 and R_2;

Y is a chain of 0-4 amino acids, inclusive the C-terminal one of which bonds to R3 and R4;

R_1 is H, C_1 -C_{12} alkyl, C_6 -C_{18} aryl, C_1 -C_{12} acyl, C_7 -C_{18} aralkyl, or C_7 -C_{18} alkaryl;

Y is a chain of 0-4 amino acids, inclusive, the C-terminal one of which is bonded to R_3 and R_4;

R_1 is H, C_1-C_{12} alkyl (e.g. methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl);

R_2 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl);

A^{22} is an aromatic amino acid, Ala, Aib, Anb, N-Me-Ala, or is deleted;

A^{23} is Ser, Thr, Ala, Aib, N-Me-Ser, N-Me-Thr, N Me-Ala, or is deleted;

A^{24} is leu, Ile, Val, Trp, Gly, Nle, Nva, Aib, Anb, N-Me-Leu, or is deleted;

A^{25} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lye-e-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or an aryl group), Orn, or is deleted;

A^{26} is Ala, His, Thr, 3-Me-His, 1-Me-His, β-pyrozolylalanine, N-Me-His, Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl groups or an aryl group), Orn, or is deleted;

A^{27} is an aromatic amino acid other than Tyr;

A^{28} is Leu, Ile, Val, Trp, Nle, Nva, Aib, Anb, or N-Me-Leu;

A^{29} is Asn, Ala, Gin, Gly, Trp, or N-Me-Asn;

A^{30} is Leu, Ile, Val, Trp, Nle, Nva, Aib, Anb, or N-Me-Leu;

~~A^{31} is Val, Leu, Ile, Trp, Nle, Nva, Aib, Anb, or N-Me-Val;~~

A^{32} is Thr, Ser, N-Me-Ser, N-Me-Thr, or D-Trp;

R_3 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl); and

R_4 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl), or a pharmaceutically acceptable salt thereof.

In preferred embodiments, A^{27} is Phe, Nal, Bip, Pcp, Tic, Trp, Bth, Thi, or Dip.

In preferred embodiments X is A^{17}-A^{18}-A^{19}-A^{20}-A^{21} wherein

R_1 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl);

R_2 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl);

A^{25} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or an aryl group), Orn, or is deleted;

A^{26} is Ala, His, Thr, 3-Me-His, 1-Me-His, β-pyrozolylalanine, N-Me-His, Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl groups or an aryl group), Orn, or is deleted;

A^{27} is an aromatic amino acid;

A^{28} is Leu, Ile, Val, Trp, Nle, Nva, Aib, Anb, or N-Me-Leu;

A^{29} is Asn, Ala, Gin, Gly, Trp, or N-Me-Asn;

A^{30} is Leu, Ile, Val, Trp, Nle, Nva, Aib, Anb, or N-Me-Leu;

A^{31} is Val, Ile, Trp, Nle, Nva, Aib, Anb, or N-Me-Val;

A^{32} is Thr, Ser, N-Me-Ser, N-Me-Thr, or D-Trp;

R_3 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl); and

R_4 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl), or a pharmaceutically acceptable salt thereof. See U.S. Patent No. 5,604,203.

In particular embodiments, A^{27} is Phe, Nal, Bip, Pcp, Tic, Trp, Bth, Thi, or Dip.

In particular embodiments X is A^{33}-A^{34}-A^{35}-A^{36} wherein

A^{33} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or C_6-C_{18} aryl group), Cys, or Orn;

A^{34} is Gln, Asn, Ala, Gly, N-Me-Gin, Aib, Cys, or Anb;

N-α-Ac-ASLRH[Bth]LNLVTRQRY-NH_2	(SEQ ID NO: 273)
N-α-Ac-[Trp^{27}]PYY (22-36)	(SEQ ID NO: 274)
N-α-Ac-ASLRH[Trp]LNLVTRQRY-NH_2	(SEQ ID NO: 275)
N-α-Ac-[Thi^{27}]PYY (22-36)	
N-α-Ac-ASLRN[Thi]LNLVTRQRY-NH_2	(SEQ ID NO: 276)
N-α-Ac-[Tic^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Tic]LNLVTRQRY-NH_2	(SEQ ID NO: 277)
N-α-Ac-[Phe^{27}]PYY (25-36)	
N-α-Ac-H[Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 279)
N-α-Ac-[Phe^{27},Thi^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Phe]LNLVTRQR[Thi]-NH_2	(SEQ ID NO: 280)
N-α-Ac-[Thz^{26},Phe^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Thz][Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 281)
N-α-Ac-[Phe^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Thz][Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 282)
N-α-Ac-[Phe^{27}]PYY (22-36)	
N-α-Ac-[Phe]SLRN[Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 289)
N-α-Ac-[Tyr^{22},Phe^{27}]PYY (22-36)	
N-α-Ac-[Tyr]SLRH[Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 290)
N-α-Ac-[Trp^{28}]PYY (22-36)	
N-α-Ac-ASLRHY[Trp]NLVTRQRY-NH_2	(SEQ ID NO: 291)
N-α-Ac-[Trp^{28}]PYY (22-36)	
N-α-Ac-ASLRHYLN[Trp]VTRQRY-NH_2	(SEQ ID NO: 292)
N-α-Ac-[Ala^{26},Phe^{27}]PYY (22-36)	
N-α-Ac-ASLR[Ala][Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 293)
N-α-Ac-[Bth^{27}]PYY (22-36)	
N-α-Ac-ASLR[Bth]LNLVTRQRY-NH_2	(SEQ ID NO: 294)
N-α-Ac-[Phe^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 295)
N-α-Ac-[$Phe^{27,36}$]PYY (22-36)	
N-α-Ac-ASLRH[Phe]LNLVTRQR[Phe]-NH_2	(SEQ ID NO: 296)
N-α-Ac-[Phe^{27}, D-Trp^{32}]PYY (22-36)	
N-α-Ac-ASLRH[Phe]LNLV[D-Trp]RQRY-NH_2	(SEQ ID NO: 297)

Other PYY agonists include neurophilic Y Y2 receptor specific peptides having the formula:

$X1(-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14)_n-X15$

wherein

X1 is NH, CH_3CO or one or two naturally occurring amino acids.

X2 is Leu, Ile or Val.

X3 is Arg, Lys or His.

X4 is His, Lys or Arg.

ψ is a pseudopeptide bond selected from the group consisting of --CH_2 --NH--, --CH_2 --S--, --CH_2 --CH_2 --, --CH_2 --O-- and --CH_2 --CO--. See U.S. Patent No. 6,046,162.

Particular compounds of the immediately foregoing group of compounds are where R^1 is acetyl and ψ is --CH_2 --NH--.

A particular group of compounds is selected from a group consisting of N-α-Ac-[$Nle^{24,28,30}$, Trp^{27}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 302)

N-α-Ac-[$Nle^{24,28}$, $Trp^{27,30}$, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 303)

N-α-Ac-[$Nle^{24,28,30}$, Phe^{27}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 304)

N-α-Ac-[$Nle^{24,28}$, Phe^{27}, Trp^{30}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 305)

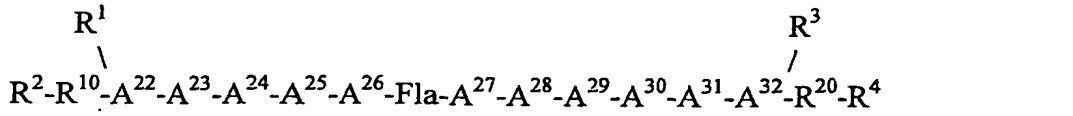
N-α-Ac-[Trp^{30}, $\psi^{35/36}$]PYY(25-36)-NH_2, (SEQ ID NO: 306)

N-α-Ac-[Trp^{30}]PYY(25-36)-NH_2 (SEQ ID NO: 307) and

N-α-Ac-[Nle^{28}, Trp^{30}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 308) or a pharmaceutically acceptable salt thereof.

Another particular compound has the formula N-α-Ac-[$Nle^{24,28}$, Trp^{30}, Nva.sup.31, $\psi^{35/36}$]PYY(22-36)-NH_2 (SEQ. ID. NO: 309) or a pharmaceutically acceptable salt thereof.

Another PYY agonist has the formula (A),



having one or two pseudopeptide bonds where each pseudopeptide bond is independently selected from the group consisting of --CH_2 --NH--, --CH_2 --S--, --CH_2 --CH_2 --, --CH_2 --O-- and -CH_2 --CO--; wherein:

R^{20} is A^{33} -A^{34} -A^{35} -A^{36},

A^{33} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R^5, Cys or Orn;

A^{34} is Cys, Gin, Asn, Ala, Gly, N-Me-Gln, Aib or Anb;

A^{35} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R^5, Cys or Orn; and

A^{36} is an aromatic amino acid or Cys;

where R^5 for each occurrence is independently selected from the group consisting of H_1 (C_1 -C_{10})alkyl and (C_6 -C_{18}) aryl.

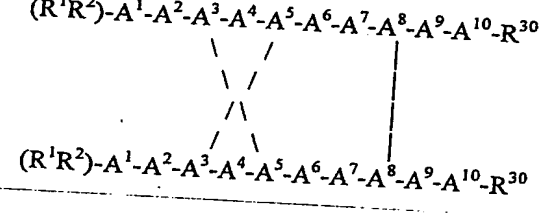
A particular group of compounds of the foregoing group of compounds are the compounds of the formula N-α-Ac-[Fla^{27})]PYY(25-36)-NH_2 and N-α-Ac-[Fla^{27}]PYY(22-36)-NH_2 or a pharmaceutically acceptable salt thereof.

Another group of PYY agonist has the formula:

(I)

$(R^1 R^2)$-A^1 -A^2 -A^3 -A^4 -A^5 -A^6 -A^7 -A^8 -A^9 -A^{10} -R^{30},

(II)

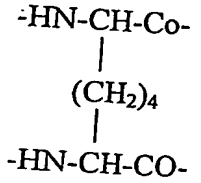


(III)

$(R^1 R^2)$-[A^5 -A^6 -A^7 -A^8 -A^9 -A^{10}]$_m$ R^{30},

or a pharmaceutically acceptable salt thereof wherein

------represents an optional bond between the amino acids shown connected where each bond is independently selected from the group consisting of --S--S-- only when the amino acids connected are Cys-Cys, -CO-NH-, -CH_2 -NH- and



A^7 is deleted or D- or L- of the following amino acids: Arg, Lys, homo-Arg, dialkyl-homo-Arg, Lys-ε-NH-R^7 or Orn;

A^8 is deleted or D- or L- of the following amino acids: Nva, Val, Ile, Leu, Nle, Anb, Aib, Pro, Gln, Asn, Glu, Asp, Orn, Lys, Dpr or Cys;

A^9 is deleted or D- or L- of the following amino acids: Arg, Lys, homo-Arg, dialkyl-homo-Arg, Lys-ε-NH-R^7 or Orn; and

A^{10} is deleted or D- or L- of the following amino acids: Tyr, Trp, Fla, Bth, Nal, Tic, Tic-OH, Dip, Bip, tyramine or optionally substituted Phe where the Phe is optionally substituted with one to five substituents selected from the group consisting of (C_1 -C_4)alkyl, halo, (C_1 -C_4)alkoxy, amino and nitro, or the corresponding decarboxylated optionally substituted Phe;

where R^7 for each occurrence is independently selected from the group consisting of H.sub.-1 (C_1 -C_{10})alkyl and (C_6 -C_{18}) aryl, provided that not all of A_1 to A_{10} are deleted at the same time. See U.S. Patent No. 6,046,167.

A particular group of compounds of the immediately foregoing group of compounds is

(SEQ ID NO: 310)

H--Ile--Asn--Pro--Ile--Tyr--Arg--Leu--Arg--Tyr--OMe

(SEQ ID NO: 311)

H--Ile--Asn--Pro--Cys--Tyr--Arg--Leu--Arg--Tyr—Ome

|

H--Ile--Asn--Pro--Cys--Tyr--Arg--Leu--Arg--Tyr--Ome,

(SEQ ID NO: 312)

H--Cys--Tyr--Arg--Leu--Arg--Tyr—Ome

|

H--Cys--Tyr--Arg--Leu--Arg--Tyr--OMe,

(SEQ ID NO: 313)

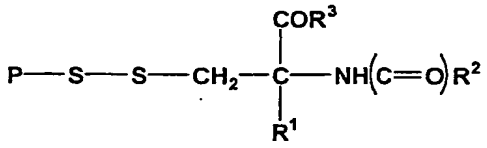
H--Ile--Asn--Pro--NH--CH--CO--Tyr--Arg--Leu--Arg--Tyr--OMe

|

$(CH_2)_4$

turnover, and become released into interstitial fluid as the result of disulfide bond reduction.

Such lipidized PYY and PYY agonist compounds have the general formula



in which P is a residue derived from a PYY or PYY agonist; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety and R^3 is --OH, a lipid-containing moiety or an amino acid chain comprising one or 2 amino acids and terminating in $-CO_2H$ or $-COR^2$. See U.S. Patent No. 5,936,092. These conjugates are particularly useful for increasing the absorption and prolonging blood and tissue retention of PYY and PYY agonists.

Typical alkyl groups include C_{1-6} alkyl groups including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, and the like.

Preferred aryl groups are C_{6-14} aryl groups and typically include phenyl, naphthyl, fluorenyl, phenanthryl, and anthracyl groups.

The term "lipid-containing moiety" refers to either a lipid group per se or a hydrocarbon-based group (in particular, one or more amino acids) comprising a lipid group. By the term "lipid group" is meant a hydrophobic substituent consisting of 4 to 26 carbon atoms, preferably 5 to 19 carbon atoms. Suitable lipid groups include, but are not limited to, the following: palmityl ($C_{15}H_{31}$,), oleyl ($C_{15}H_{29}$), stearyl ($C_{17}H_{35}$), cholate; and deoxycholate.

PCT Application No. WO 00/34236 describes drug-carrier conjugates and synthetic strategies for their production, as well as synthetic methods, intermediates, and final products useful for the uptake and release of biologically-active amino group containing compounds. Such lipidized PYY and PYY agonist compounds have general Formula I

1-6, for example, tolyl, o-, m-, and p-xylyl, ethylphenyl, 1-propylphenyl, 2-propylphenyl, 1-butylphenyl, 2-butylphenyl, t-butylphenyl, 1-pentylphenyl, 2-pentylphenyl, 3-pentylphenyl.

Typical alkenyl groups include C_{2-6} alkenyl groups, e.g. ethenyl, 2-propenyl, isopropenyl, 2-butenyl, 3-butenyl, 4-pentenyl, 3-pentenyl, 2-pentenyl, 5-hexenyl, 4-hexenyl, 3-hexenyl, and 2-hexenyl groups.

Typical alkynyl groups include C_{2-6} alkynyl groups e.g. enthynyl, 2-propenyl, 2-butynyl, 3-butynyl, 4-pentynyl, 3-pentynyl, 2-pentynyl, 5-hexynyl, 4hexynyl, 3-hexynyl, and 2-hexynyl groups.

Typical alkenyl or alkynyl substituted aryl groups include any of the above C_{6-14} aryl groups substituted by any of the above C_{2-6} alkenyl or C_{2-6} alkynyl groups, e.g., ethenylphenyl, 1-propenylphenyl, 2-propenylphenyl, 1butenylphenyl, 2-butenylphenyl, 1-pentenylphenyl, 2-pentenylphenyl, 3-pentenylphenyl, 1-hexenylphenyl, 2-hexenylphenyl, 3-hexenylphenyl, ethynylphenyl, 1-propynylphenyl, 2-propynylphenyl, 1-butynylphenyl, 2-butynylphenyl, 1-pentynylphenyl, 2-pentynylphenyl, 3-pentynylphenyl, 1-hexynylphenyl, 2-hexynylphenyl, 3-hexynylphenyl groups.

Typical halo groups include fluorine, chlorine, bromine, and iodine.

Typical halo substituted alkyl groups include C_{1-6} alkyl groups substituted by one or more fluorine, chlorine, bromine, or iodine atoms, e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, and trichloromethyl groups.

Typical alkanoyl groups include $C_{1-5}C(=O)$– alkanoyl groups, e.g., acetyl, propionyl, butanoyl, pentanoyl, and hexanoyl groups, or by an arylalkanoyl group, e.g., a $C_{1-5}C(=O)$ – alkanoyl group substituted by any of the above aryl groups.

Typical cycloalkyl groups include C_{3-8} cycloalkyl groups including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups.

The term "lipophilic group" as used herein refers to either a naturally occurring lipid per se, a hydrophobic branched or unbranched hydrocarbon comprising about 4 to about 26 carbon atoms, preferably about 5 to about 19 carbon atoms, a fatty acid or ester thereof, or a surfactant. Suitable lipophilic groups

to form a covalent bond. Although "pegylation" is often carried out using poly(ethylene glycol) or derivatives thereof, such as methoxy poly(ethylene glycol), the term is not intended to be so limited here, but is intended to include any other useful poly(alkylene glycol), such as, for example poly(propylene glycol).

The chemical moieties for derivitization may also be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72, 1996; Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750, 1999; and Caliceti et al., *Bioconjug. Chem.* 10:638-646, 1999.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the polypeptides or proteins with consideration of effects on functional

by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins and polypeptides may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein or polypeptide either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins and polypeptides are described in Delgado et al., *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304, 1992; Francis et al., *Intern. J. of Hematol.* 68:1-18, 1998; U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466.

One system for attaching polyethylene glycol directly to amino acid residues of proteins and polypeptides without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of the protein or polypeptide with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein or polypeptide. Thus, the disclosure includes protein-polyethylene glycol conjugates produced by reacting proteins and polypeptides with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

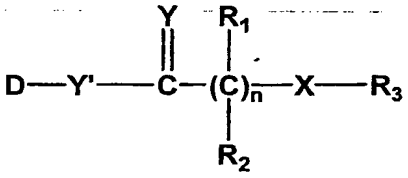
Polyethylene glycol can also be attached to proteins and polypeptides using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460 discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein or polypeptide by a linker can also be produced by reaction of proteins or polypeptides with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG- ρ -nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins and polypeptides are described in WO 98/32466.

embodiment, the hydroxyl end groups of poly(alkylene glycols) are converted and activated into reactive functional groups.

In another aspect of the disclosure, the polymer is conjugated to a facilitator moiety prior to being introduced into the polypeptide or protein molecule. The facilitator moiety is preferably an amino acid such as lysine, however, non-amino acid moieties are also contemplated. Within the aspect, there are included multifunctionalized organic moieties such as alkyls or substituted alkyls. Such moieties can be prepared to have a nucleophilic functional group such as an amine and an electrophilic group such as an acid as well as a suitably functionalized region for conjugating with the desired polymer or polymers.

The facilitator moieties allow easier inclusion of a polymer into the peptide or protein molecule during synthesis. For example, poly(alkylene glycols) coupled to facilitator amino acids or amino acid residues in polypeptides or proteins by means of suitable coupling agents are illustrative. A useful review of a number of coupling agents known in the art appears in Dreborg et al., *Critical Reviews in Therapeutic Drug Carrier Systems* 6(4):315-165, 1990, see especially, pp. 317-320.

Pegylated PYY peptides and agonists can also be of the general formula



wherein:

D is a residue of a PYY peptide or agonist;

X is an electron withdrawing group;

Y and Y' are independently O or S;

(n) is zero (0) or a positive integer, preferably from 1 to about 12;

R_1 and R_2 are independently selected from the group consisting of H, C_{1-6} alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C_{1-6} alkyls;

R_3 is a substantially non-antigenic polymer, C_{1-12} straight or branched alkyl or substituted alkyl, C_{5-8} cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or

terminal amino and/or C-terminal carboxyl group) resulting in a peptide which acts as an antagonist to a Y receptor. In addition, PYY, NPY, or PP amino acid sequences may be fusion or chimera proteins which act as antagonists at the Y receptor. These peptides may also be modified by processes such as, lipidation, pegylation, amidation, glycosylation, acylation, sulfation, phosphorylation, acetylation and cyclization.

Many non-peptide antagonist of the Y receptors are known in the art and are contemplated for use with this invention. (See Table 5, *infra*). Any known PYY, NPY, or PP non-peptide antagonist may be useful in this invention.

TABLE 5 – PYY AND NPY ANTAGONIST

Exemplary antagonists of the Y receptor include, but are not limited to the following:

BIBO3304

Ref: Berglund, MM. *Biochem Pharmacol* 60(12):1815-22, Dec 15, 2000.

SR120819A

1-[2-[2-(2-naphtylsulfamoyl)-3-phenylpropionamido]-3-[4-[N- [4-(dimethylaminomethyl)-cis-cyclohexylmethyl]amidino]phenyl]propiony l] pyrrolidine, (S,R) stereoisomer

Ref: Berglund, MM. *Biochem Pharmacol* 60(12):1815-22, Dec 15, 2000.

BIIE0246

(S)-N2-[[1-[2-[4-[(R,S)-5,11-dihydro-6(6h)-oxodibenz[b,e]azepin-11-yl]-1-piperazinyl]-2-oxoethyl]cyclopentyl]acetyl]-N-[2-[1,2-dihydro-3,5 (4H)-dioxo-1,2-diphenyl-3H-1,2,4-triazol-4-yl]ethyl]-argininamid

Ref: Malmstrom, *Life Sci* 69(17):1999-2005, Sep 14, 2001.

Alkyl and cycloalkyl derivatives of 1,4-dihydropyridine

(e.g., 1,4-dihydro-2,6-dimethyl-4-[4-[[[[3-[4-(3-methoxyphenyl)-1-piperidinyl]prop yl]amino]carbonyl]amino]butyl]-3,5-pyridine dicarboxylic acid, dimethyl ester)

Ref: U.S. Patent No. 6,444,675

4-(3-substituted-phenyl)-1,4-dihydropyridine derivatives

Ref: U.S. Pat. No. 5,635,503

Squarate derivatives of 4-phenyl-1,4-dihydropyridines

e.g., 1,4-dihydro-4-[3-[[2-[[3-[4-(3-methoxyphenyl)-1-piperidinyl]propyl]amino]-3 ,4-dioxo-1-cyclobuten-1-yl]amino]phenyl]-2,3-dimethyl-3,5-pyridinedicarboxy lic acid, dimethyl ester

Ref: U.S. Patent No. 6,432,960

N-(9-Ethyl-9H-carbazol-3-yl)-3-(4-piperidin-1-ylmethyl-phenoxy)-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-3-[methyl-(1,2,3,4-tetrahydro-naphthalen-2-yl) -amino]-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-3-(quinolin-7-yloxy)-propionamide; and

2-[Bis-(2-hydroxy-ethyl)-amino]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide.

3-Bromo-N-(9-ethyl-9H-carbazol-3-yl)-propionamide; N-(9-Isopropyl-9H-carbazol-3-yl)-trifluoroacetamide;

4-Dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)-N-methyl-butyramide;

N-(9-Methyl-9H-carbazol-3-yl)-trifluoroacetamide;

1-Hydroxy-cyclopropanecarboxylic acid (9-ethyl-9H-carbazol-3-yl)-amide; and

2-(4-Chloro)-benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide.

2-(4-fluoro)-benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

(R)-N-(9-Ethyl-9H-carbazol-3-yl)-2-(1-phenyl-ethylamino)-acetamide;

(R)-N-(9-Ethyl-9H-carbazol-3-yl)-2-(1-(4-chloro)-phenyl-ethylamino)-acetamide;

2-(3-Diethylamino-2-hydroxy-propylamino)-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

2-(Benzyl-isopropyl-amino)-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

N-3-Bromo-(9-ethyl-9H-carbazol-6-yl)-trifluoroacetamide;

N-(9-Ethyl-6-formyl-9H-carbazol-3-yl)-trifluoroacetamide;

N-(9-Ethyl-6-hydroxymethyl-9H-carbazol-3-yl)-trifluoroacetamide;

N-(9-Ethyl-9H-carbazol-3-yl)-methanesulfonamide;

N-(9-Ethyl-9H-carbazol-3-yl)-chloromethanesulfonamide;

2-Bromo-N-(9-ethyl-9H-carbazol-3-yl)-acetamide; and

3-Dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)-propionamide.

2-[Bis-(2-hydroxy-ethyl)-amino]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

2-Benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

Various dihydropyridine derivatives:

Ref: U.S. Patent No. 4,829,076

Cyanoguanidine derivatives of the 4-(3-substituted-phenyl)-1,4-dihydropyridines

Ref: U.S. Patent No. 6,001,836

Amide derivatives that are NPY Y5 receptor antagonists

Ref: U.S. Patent No. 6,410,792

Thiourea linked piperazine and piperidine derivatives of 4-phenyl-1,4-dihydropyridines, such as:

1,4-dihydro-4-[3-[[[[3-[4-(3-methoxyphenyl)piperidinyl]propyl]amino]carbono thioyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-(4-phenylpiperidinyl)propyl]amino]carbonothioyl]amin o]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester, and

1,4-dihydro-4-[4-[[[[3-(4-cyclohexyl-1-piperazinyl)propyl]amino]carbonothio yl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester.

1,4-dihydro-4-[4-fluoro-3-[[[[3-(4-phenylpiperidinyl)propyl]amino]carbonoth ioyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-(4-methyl-1-piperidinyl)propyl]amino]carbonothioyl]a mino]-4-fluorophenyl)-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-(4-ethyl-1-piperidinyl]propyl]amino]carbonothioyl]am ino]-4-fluorophenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-(4-propyl-1-piperidinyl)propyl]amino]carbonothioyl]a

4-Oxo-1-phenyl-N-[cis-1,2,3,4-tetrahydro-1-(3-pyridinylmethyl)-2-naphthalenyl]-1,3,8-triazaspiro[4.5]decane-8-acetamide bis-hydrochloride,

trans-N-[2-(4-fluorophenyl)-3-(3-pyridinyl)propyl]-4-[((2-fluorophenylsulfonyl)amino)methyl]-1-cyclohexanamide hydrochloride,

trans-N-[[[[[2-(4-fluorophenyl)-3-(3-pyridinyl)propyl]amino]methyl]-4-cyclo hexyl]methyl] 2-fluorobenzenesulfonamide bis-hydrochloride.

Ref: U.S. Patent No. 6,380,224.

Alkylene diamine-substituted pyrazlo (1,5-a)-1,5-pyrimidines and pyrazolo (1,5-a) 1,3,5-triazines, such as:

2-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-butan-1-ol;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-methyl-cyclohexane-1,4-diamine;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-ethyl-cyclohexane-1,4-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(4-morpholin-4-yl-cyclohexyl)-ethane-1,2-diamine;

4-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-cyclohexanol;

3-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-propane-1,2-diol;

N-{2-[3(2,6-dichloro-4-methoxy-phenyl)-2,5-dimnethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-isobutyl-cyclohexane-1,4-diamine;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N-isobutyl-cyclohexane-1,4-diamine;

4-{2-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-1-methyl-ethylamino}-cyclohexanol;

2-{2-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-cyclohexanol;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazol[1,5-a]pyrimidin-7-yl]-N-(4,4,4-trifluoro-butyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-isopropyl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N-(2,2,6,6-tetramethyl-piperidin-4-yl)ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-ethyl-piperidin-3-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4methoxy-phenyl)-2, 5-dimethyl-pyrazol to [1, 5-a] pyrimidin-7-yl]-N'-piperidin-4-yl-ethane 1,2-diamine;

N.sup.2 -(1-Benzyl-piperidin-4-yl)-N'-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazo lo[1,5-ajpyrimidin-7-yl]-propane-1,2-diamine;

N-[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyridin-3-ylmethyl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-Dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(1-pyridin-4-ylmethyl-piperidin4-yl)-ethane-1,2-diamine;

3,5-Dichloro-4-12,5-dimethyl-7-[2-(1-phenyl-pyrrolidin-3-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl]-phenol;

N-[3-(2,6-dicloro-4-methoxy-phenyl)-2,5-dimethyl-purazolo[1,5-a]pyrimdin-7-yl]-N'-(1-pyridin-2-ylmethyl-piperidin-4-yl)-ethane-1,2-diamine;

3,5-dichloro-4-(2,5-dimethyl-7-[2-(1-pyrimidin-2-yl-piperidin-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile;

N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5 a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-(1-benzyl-piperidin-4-yl)-N'-[3(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-5isopropyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)ethane-1,2-diamine;

N-[3-(2,4-dichloro-phenyl)-5-isopropyl-2-methyl-pyrazolo[1,5a]pyrimidin-7-y l]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-ylpiperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,4-dimethyl-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,4-dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine; and

1-[4-(1-{[3-(2,6-dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-methyl]-propylamino)piperidin-1-yl]-ethanone.

N-[2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N-[2-(4-methoxy-phenyl)-ethyl]-ethane-1,2diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo1,5-a]pyrimidin-7-yl]-N-[2-(4-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-[2-(3-ethoxy-4-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo 1,5-a]pyrimidin-7-yl]-N-[2-(4-ethoxy-3-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,a]pyrimidin-7-yl]-N'-(1,2,3,4-tetrahydro-naphthalen-2-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2-pyridin-2-yl-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2-pyridin-3-yl-ethyl)-ethane-1,2-diamine; and

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N-(2-pyridin4-yl-ethyl)-ethane-1,2-diamine.

Ref: U.S. Patent No. 6,372,743

Spiroisoquinolinone derivative Y antaponist, such as:

2-(3-Chloropropyl)-2-phenyl-1,3-dioxolane,

2-(3-Chloropropyl)-2-(4-methoxyphenyl)-1,3-dioxolane,

2-(3-Chloropropyl)-2-(4-phenoxyphenyl)-1,3-dioxolane,

2-(3-Chloropropyl)-2-(4-bromophenyl)-1,3-dioxolane,

1'-[4-[(1,1'-Biphenyl)-4-yl]-4-oxobutyl]spiro[isoquinoline-1-(2H)4'-piperidine-3-(4H)-one] Hydrochloride,

1'-[2-[(1,1'-Biphenyl)-4-yl]-2-hydroxyethyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3-(4H-one] Hydrochloride,

Ref: U.S. Patent No. 6,348,472

Triazine derivative Y receptor antagonists, such as:

N1-{[4-({[4-(Isopropylamino)-6-(methylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4-(ethylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide)-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfenamideN1-{[4-({[4,6-Di(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4-(isopropylamino)-6-(propylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl3methyl-1-naphthalenesulfonamide,

N1-[4-([4-(butylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(cyclobutylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(cyclopropylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(isopropylamino)-6-(pentylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-[(2-cyanoethyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-[(2-hydroxyethyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-(4-[(4-(isopropylamino)-6-((2-methoxyethyl)amino]-1,3,5-triazin-2-yl]amino)methyl]cyclohexylmethyl)-1-naphthalenesulfonamide,

N1-{[4-({[4-(isopropylamino)-6-(4-isopropylpiperazino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl -4-(tert-butyl)-1-benzenesulfonamide,

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl -4-fluoro-1-benzenesulfonamide,

N1-[4-([4,6-di (ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-methoxy-5-methyl-1-benzenesulfonamide, N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-fluoro-1-benzenesulfonamide,

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-methyl-1-benzenesulfonamide, N3-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-3-pyridinesulfonamide, N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-4-methoxy-1-benzenesulfonamide,

N5-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2,4-dimethyl-1,3-oxazole-5-sulfonamide, N2-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-thiophenesulfonamide, N4-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-methyl-1H-4-imidazolesulfonamide, N1-4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl- 4-methyl-1-benzenesulfonamide, N5-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl -2,1,3-benzothiadiazole-5-sulfonamide, N8-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl -8-quinolinesulfonamide-yl]aminomethyl)cyclohexyl]methylme thanesulfonamide N1-[4-([4-(isopropylamino)-6-tetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-pyrrolidinesulfonamide,

N4-[4-([4-(isopropylamino)-6-morpholino-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-4-morpholinesulfonamide,

N1-[4-([4-(isopropylamino)-6-piperidino-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-piperidinesulfonamide,

1-Aza-9-fluoro-4,5-dihydro-2-{5-(dimethylaminosulfonyl-amino)pentyl}amino-3 -thia-benzo[e]azulene;

1-Aza-9-fluoro-2-(5-(2-fluorophenyl)sulfonylamino)pentylamino-4,5-dihydro-3 -thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(1-naphthyl)sulfonylamino)-pentylamino-3-th ia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-(methanesulfonylamino)-butyl)amino-3-thia-b enzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-(dimethylaminosulfonyl-amino)butyl)amino-3- thia-benzo[e]azulene;

1-Aza-9-fluoro-2-(4-(2-fluorophenyl)sulfonylamino)butylamino-4,5-dihydro-3- thia-benzo[e]azulene -3-thia -benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-((2(S)-methoxymethyl)-pyrrolidine-1-yl)sulfonyl)phenylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(methylsulfonylamino)-pentyl)amino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(methylsulfonylamino-methyl)cyclohexyl)amino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(2,4-difluorophenyl)sulfonylamino)pentylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-isopropylsulfonylamino)-pentylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(diethylaminosulfonyl-amino)pentyl)amino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(2-methoxy-5-methylphenyl)sulfonylamino)pen tylamino-3-thia-benzo[e]azulene;

1-Aza-2-(5-benzylsulfonylamino)pentylamino-9-fluoro-4,5-dihydro-3-thia-benz o[e]azulene;

1-Aza-2-(5-(3,4-difluorophenyl)sulfonylamino)pentylamino-9-fluoro-4,5-dihyd ro-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(4-methoxyphenyl)sulfonylamino)pentylamino- 3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-diethylaminosulfonylamino)-cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(4-methoxyphenyl)sulfonylamino)-cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2-thienyl)sulfonyl-amino)-cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2,2,2-trifluoro-ethyl)sulfonylamino)-cyclohexylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-(2,2,2-trifluoroethyl)-sulfonylamino)butylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-2-{4-(3,4-difluorophenyl)sulfonyl-aminomethy}cyclohexy lamino-4,5-dihydro-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-2-{4-trifluoromethylsulfonylaminomethyl}cyclohexylamino-4,5-dihydro-3-thiabenzo[e]-azulene;

trans-1-Aza-9-fluoro-2-{4-(2-fluoro)phenylsulfonylamino}-cyclohexylmethylamino-4,5-dihydro-3-thia-benzo[e]azulene;

trans-N2-(4-Methylsulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine: A mixture of trans-N2-(4-amino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclo hepta[d][1,3]thiazol-2-aminedihydrochloride;

trans-N2-(4-Aminosulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-N2-(4-Amino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-N2-(4-Aminosulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine: 6-Bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one;

N1-(9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)-5-bromopentanamide;

1-Aza-9-fluoro-4,5-dihydro-2-{2-[2-(2-methoxy-5-methylphenyl)sulfonylamino] ethoxy}ethylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(3-pyridyl)sulfonylaminomethyl)cyclohexylamino-3-thia-benzo[e]azulene;

trans-N2-(4-Ethylsulfonylamino)cyclohexylmethyl-8-methoxy-4,5-dihydro-benzo [2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

trans-1-Aza-4,5-dihydro-8-methoxy-2-{4-methylsulfonyl-amino)cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(3-pyridyl)sulfonylamino}cyclohexylmethylamino-3-thia-benzo[e]azulene;

trans-1-Aza-4,5-dihydro-9-methoxy-2-{4-methylsulfonyl-amino}cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene;

trans-N2-(4-Ethylsulfonylamino)cyclohexylmethyl-9-methoxy-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

trans-N2-(4-Methylsulfonylamino)cyclohexylmethyl-7-methoxy-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine hydrochloride;

trans-1-Aza-4,5-dihydro-7-methoxy-2-{4-dimethylaminosulfonylamino}cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene;

trans-N2-(4-Dimethylphosphonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4 H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-N2-(4-Ethoxycarbonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine hydrochloride;

1-Aza-9-fluoro-4,5-dihydro-2-(2-(2-isopropylsulfonylamino)-ethoxy)ethylamino-3-thia-benzo[e]-azulene;

2-(4-Methylsulfonylaminomethyl)cyclohexylamino-4H-chromeno[4,3-d]thiazole;

trans-1-Aza-4,5-dihydro-8-methoxy-2-(4-methylsulfonyl-amino)cyclohexylmethylamino-3-thia-benzo[e]-azulene;

trans-1-Aza-4,5-dihydro-8-methoxy-2-(4-methylsulfonylamino-methyl)cyclohexylamino-3-thia-benzo[e]-azulene;

N1-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]thiazol-2-yl) amino]cyclohexyl}methyl)-2-methoxyacetamide;

N1-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta-[d][1,3]thiazol-2-yl)amino]cyclohexyl}methyl)acetamide;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(N-propylformamido)-methyl)cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(N-isopropylformamido)methyl)cyclohex ylamino-3-thia-benzo[e]azulene;

N1-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-2-methoxyacetamide;

Benzyl-N-(4-{[(aminocarbothioyl)amino]methyl}cyclohexyl)-carbamate;

Benzyl-N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}carbamate;

N2-[(4-aminocyclohexyl)methyl]-4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine

N-{[4-(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-N-propylformamide;

N1-{[4-(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}propanamide;

N2-{4-[(Propylamino)methyl]cyclohexyl}-4,5-dihydrobenzo-[2,3]oxepino[4,5-d] [1,3]thiazol-2-amine;

N-{[4-(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-N-propylformamide;

N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-(2-methoxyethyl)formamide;

N2-({4-[(2-methoxyethyl)amino]cyclohexyl}methyl)-4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-(2-methoxyethyl)formamide;

trans-1-Aza-2-(4-(n-(ethyl)formamido)cyclohexyl)methyl-amino-4,5-dihydro-6-oxa-3-thia-benzo[e]azulene;

4-(2-Pyridyl)-2-(5-(2-thienyl)sulfonylaminopentyl)-amino-thiazole hydrogen chloride

2-(5-(2-Fluorophenyl)sulfonylamino)pentylamino-4-(2-pyridyl)-thiazole hydrogen chloride

2-(5-(4-Methoxyphenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(3,4-Difluorophenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(2-Methoxy-5-methylphenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(Benzylsulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(Ethylsulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(Trifluoromethylsulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(Aminosulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(2-Fluorophenyl)sulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride

2-(5-(2-Methoxy-5-methyl)phenylsulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride

2-(5-(2-Fluoro)phenylsulfonylamino)pentylamino-4-(4-pyridyl)thiazole hydrogen chloride

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(4-pyridyl)thiazole hydrogen chloride 2-(5-(2-Methoxy-5-methyl)phenylsulfonylamino)pentylamino-4-(4-pyridyl)thiazole hydrogen chloride

trans-N,N-dimethyl-N'-[(4-[4-(-1,3-thiazol-2-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]sulfamide

N,N-Dimethyl-N'-(5-{[4-(2-thienyl)-1,3-thiazol-2-yl]amino}-pentyl)sulfamide

N1-(5-{[4-(2-Thienyl)-1,3-thiazol-2-yl]amino}pentyl)-2-methoxy-5-methyl-1-b enzenesulfonamide

N1-(5-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminopentyl)-2-me thoxy-5-methyl-1-benzenesulfonamide

N1-(5-[4-(2,5-Dimethyl-1,3-thlazol-4-yl)-1,3-thiazol-2-yl]aminopentyl)-4-fluoro-1-benzenesulfonamide

N1-(5-[4-(1,3-Thiazol-2-yl)-1,3-thiazol-2-yl]aminopentyl)-4-fluoro-1-benzenesulfonamide

N'-(5-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminopentyl)-N,N-dimethylsulfamide

trans-N1-[(4-[4-(2,5-dimethyl-1,3-thiazol-4-yl])-1,3-thiazol-2-yl]aminocyclohexyl)methyl]-4-fluoro-1-benzene-sulfonamilde

trans-N'-[(4-[4-(2,5-dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]-N,N-dimethylsulfamide

trans-N'-[4-([5-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]methyl-N,N-dimethyl-sulfamide

trans-N4-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]methyl-4-morpholine-sulfonamide

trans-N-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]-N-(2-methoxyethyl)formamide

trans-N-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]-N-isopropylformamide

Ref: U.S. Patent No. 6,218,408

N-aralkylaminotetralin Y receptor antagonist, such as:

rac-cis-1-(Phenylmethyl)-6-methoxy-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,2,3,4-tetrahydro-2-naphthalenamine;

rac-cis-1-(4-Fluorophenylmethyl)-N-(3-phenylpropyl)-1,2,3,4-tetrahydro-2-na phthalenamine monohydrobromide;

rac-cis-1-(3-pyridylmethyl)-N-(2-(3,4-dimethoxyphenyl)ethyl-1,2,3,4-tetrahydro-2-naphthalenamine monohydrobromide

Ref: U.S. Patent No. 6,201,025

Amide derivative Y receptor antagonist:

Ref: U.S. Patent No. 6,048,900

N-substituted aminotetralin Y receptor antagonist, such as:

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]4-cyclohexyl]methyl]2-naphthalenesulfo namide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]-5-pentyl]2-naphthalenesulfonamide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]2-naphthalenesulfonamide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-fluoro-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]2-fluorobenzenesulfonamide;

rac-[1α,2α (trans)]-N-[[[[[1,2,3,4-tetrahydro-6-fluoro-1-phenyl-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]2-naphthalenesulfonamide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(1-propene-3-yl)-2-naphthalenyl]amino]methyl]4-cyclohexyl]methyl] benzenesulfonamide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-hydroxypropyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide;

rac-[1α,2 α (trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(n-propyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide.

Ref: U.S. Patent No. 6,140,354

4-phenyl-1,4-dihydropyrimidinone derivative Y receptor antagonist:

Ref: U.S. Patent No. 5,889,016

1,4-Dihydro-4-[3-[[[[3-[4-(phenylmethyl)-piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

4-[3-[[[[3-(4-cyclohexyl-1-piperidinyl)propyl]amino]carbonyl]amino]phenyl]-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-dihydro-4-[3-[[[[3-[4-hydroxy-4-(2-phenoxyphenyl)-1-piperidinyl]propyl] amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-(4-phenyl-1-piperidinyl)propyl]amino]carbonyl]amino] phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, ethyl methyl ester;

1,4-Dihydro-4-[3-[[[[3-[(4-phenylmethyl)-1-piperidinyl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, ethyl methyl ester;

1,4-Dihydro-4-[3-[[[3-[4-hydroxy-4-(2-methoxyphenyl)-piperidin-1-yl]propyl] amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, ethyl methyl ester;

1. 4-Dihydro-4-[3-[[[[3-[4-hydroxy-4-(3-methoxyphenyl)-piperidin-1-yl]propy l]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, ethyl methyl ester;

1,4-Dihydro-2,6-dimethyl-4-[3-[[[[3-[4-[3-(2-propoxy)phenyl]-1-piperidinyl]-propyl]amino]carbonyl]amino]phenyl]3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[2-[4-(3-methoxyphenyl)-1-piperidinyl]ethyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester hydrochloride;

1,4-Dihydro-4-[3-[[[[4-[4-(3-methoxyphenyl)-1-piperidinyl]butyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester hydrochloride;

1,4-dihydro-4-[3-[[[[3-[4-(3-methoxyphenyl)-1-piperidinyl]propyl]oxy]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester hydrochloride;

1,4-Dihydro-4-[3-[[[[3-[4-(3-methoxyphenyl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-(2-methoxyphenyl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-(3-hydroxyphenyl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-naphthalenylpiperidin-1-yl]propyl]amino]carbonyl] amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

4-[3-[[[[3-(4-cyclohexyl-1-piperidinyl)propyl]amino]carbonyl]amino]phenyl]- 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[1,2,3,6-tetrahydro-4-(3-methoxyphenyl)pyridin-1-yl] propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[3-[1,2,3,6-tetrahydro-4-(1-naphthalenyl)pyridin-1-yl]propyl]amino]carbonyl]amino]phenyl-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester.

Ref: U.S. Patent No. 5,668,151

As disclosed herein, when administered to humans, PYY was found to reduce appetite. When infused into humans at physiological post-prandial levels, PYY_{3-36} significantly decreased appetite and reduced food intake by a third over 12 hours, and even by a third over 24 hours. Both the effect itself and the duration of the effect are surprising and unpredictable, as they occurred for many hours after the

The disclosure is illustrated by the following non-limiting Examples.

EXAMPLES

Example 1

Material and Methods

Generation of POMC-EGFP mice: The *EGFP* cassette contains its own Kozak consensus translation initiation site along with *SV40* polyadenylation signals downstream of the *EGFP* coding sequences directing proper processing of the 3' end of the EGFP mRNA. The *EGFP* cassette was introduced by standard techniques into the 5' untranslated region of exon 2 of a mouse *Pomc* genomic clone containing 13 kb of 5' and 2 kb of 3' flanking sequences (Young et al., *J Neurosci* 18, 6631-40, 1998). The transgene was microinjected into pronuclei of one-cell stage embryos of C57BL/6J mice (Jackson Laboratories) as described (Young et al., *J Neurosci* 18, 6631-40, 1998). One founder was generated and bred to wildtype C57BL/6J to produce N_1 hemizygous mice. In addition, N_2 and subsequent generations of mice homozygous for the transgene were also generated. The mice are fertile and have normal growth and development.

Immunofluorescence and GFP co-localization: Anesthetized mice were perfused transcardially with 4% paraformaldehyde and free-floating brain sections prepared with a vibratome. Sections were processed for immunofluorescence and colocalization of GFP fluorescence using standard techniques. Primary antisera and their final dilutions were rabbit anti-β-endorphin, 1:2500 v/v; rabbit anti-NPY, 1:25,000 v/v (Alanex Corp.); rabbit anti-ACTH, 1:2000 v/v; and mouse anti-TH, 1:1000 v/v (Incstar). After rinsing, sections were incubated with 10mg/ml biotinylated horse anti-mouse/rabbit IgG (Vector Laboratories) followed by Cy-3 conjugated streptavidin, 1:500 v/v (Jackson Immunoresearch Laboratories). Photomicrographs were taken on a Zeiss Axioscop using FITC and RITC filter sets (Chroma Technology Corp.).

Immunostaining for light and electron microscopy: Double immunocytochemistry for NPY and POMC using different color diaminobenzidine(DAB) chromogens was carried out on fixed mouse hypothalami according to published protocols (Horvath et al., *Neuroscience* 51, 391-9, 1992). For electron microscopy, preembedding immunostaining for β-endorphin was using an ABC Elite kit (Vector Laboratories) and a DAB reaction followed by post-embedding labeling of GABA and NPY using rabbit anti-GABA, 1:1000 v/v and gold conjugated (10 nm) goat anti-rabbit IgG or sheep anti-NPY and gold conjugated (25 nm) goat anti-sheep IgG. Finally, sections were contrasted with saturated uranyl acetate (10 minutes) and lead citrate (20-30 s) and examined using a Philips CM-10 electron microscope.

Animals: Male Wistar rats (200-250g), 7-8 weeks old (Charles River Laboratories, United Kingdom) were maintained under controlled temperature (21-23° C) and light conditions (lights on 07:00-19:00) with *ad libitum* access to water and food (RM1 diet; SDS Ltd., Witham, United Kingdom) except where stated. Arcuate and paraventricular nuclei cannulations and injections were performed as previously described (Glaum et al., *Mol. Pharmacol.* 50, 230-5, 1996; Lee et al., *J. Physiol (Lond)* 515, 439-52; 1999; Shiraishi et al., *Nutrition* 15, 576-9, 1999). Correct intranuclear cannula placement was confirmed histologically at the end of each study period (Glaum et al., *Mol. Pharmacol* 50, 230-5, 1996; Lee et al., *J. Physiol (Lond)* 515, 439-52, 1999; Shiraishi et al., *Nutrition* 15, 576-9, 1999). All animal procedures were approved under the British Home Office Animals (Scientific Procedures) Act, 1986. All injection studies on fasting animals were performed in the early light-phase (0800-0900). All dark-phase feeding studies injections were performed just prior to lights off.

Male *Pomc-EGFP* mice were studied at 5-6 weeks of age and were generated as described above. *Y2r*-null mice were generated using *Cre*-lox P

viability of the tissue was verified by a 45 minute exposure to 56 mM KCL; isotonicity was maintained by substituting K^+ for Na^+. At the end of each period, the aCSF was removed and frozen at -20° C until assayed for NPY and αMSH by radioimmunoassay.

C-fos expression: C-fos expression was measured in adult Wistar rats and Pomc-EGFP mice 2 hours after IP administration of saline or PYY_{3-36} (5μg/100g) using standard immunohistochemical techniques (Hoffman et al., *Front. Neuroendocrinol.* 14, 173-213, 1993). Data were obtained from 3 rats and 5 mice in each group. For the *Pomc*-EGFP mice 5 anatomically matched arcuate nucleus sections (Franklin et al., *The Mouse Brain in Stereotaxic Coordinates*, Academic Press, San Diego, 1997) were counted from each animal, and images acquired using a Leica TSC confocal microscope (Grove et al., *Neuroscience* 100, 731-40, 2000).

RNase protection assay (RPA): Total RNA was extracted from hypothalami (Trizol, Gibco). RPAs were performed (RPAIII kit, Ambion) using 5μg RNA and probes specific for NPY, αMSH and β actin (internal standard). For each neuropeptide, the ratio of the optical density of the neuropeptide mRNA band to that of β actin was calculated. Neuropeptide mRNA expression levels are expressed relative to saline control (mean ± s.e.m. n = 4 per group). The statistical analysis used was ANOVA, with Bonferroni post hoc analysis.

Plasma assays: Human leptin was measured using a commercially available radioimmunoassay (RIA) (Linco Research, USA). All other plasma hormone levels were measured using established in-house RIAs (Tarling et al., *Intensive Care Med.* 23, 256-260, 1997). Glucose concentrations were measured using a YSI 2300STAT analyser (Yellow Springs Instruments Inc., Ohio, USA). Plasma paracetamol levels were measured using an enzymatic colorimetric assay (Olympus AU600 analyzer).

Human Studies: PYY_{3-36} was purchased from Bachem (California, USA). The Limulus Amoebocyte Lysate assay test for pyrogen was negative and the peptide was sterile on culture. Ethical approval was obtained from the Local Research Ethics Committee (project registration 2001/6094) and the study was

Example 2

Neural Network in the Arcuate Nucleus

A strain of transgenic mice was generated expressing green fluorescent protein (EGFP Clontech), under the transcriptional control of mouse *Pomc* genomic sequences that include a region located between –13 kb and –2 kb required for accurate neuronal expression (Young et al., *J Neurosci* 18, 6631-40, 1998) (Fig. 1a). Bright green fluorescence (509 nm) was seen in the two CNS regions where POMC is produced: the ARC and the nucleus of the solitary tract. Under ultraviolet (450–480 nm) excitation POMC neurons were clearly distinguished from adjacent, non-fluorescent neurons (Fig. 1b) visualized under infrared optics. Double immunofluorescence revealed >99% cellular co-localization of EGFP and POMC peptides within the ARC (Fig. 1c). There was close apposition of both tyrosine hydroxylase (TH)- and NPY-stained terminals on EGFP-expressing POMC neurons, but no evidence of co-localization of the TH or NPY immunoreactivity with EGFP. Total fluorescent cell counts performed on coronal hypothalamic sections revealed 3148 ± 62 (mean ± SEM: n=3) POMC-EGFP neurons distributed through the entire ARC (Franklin et al., *The Mouse Brain in Stereotaxic Coordinates*, Academic Press, San Diego, 1997) (Fig. 1d). POMC neurons in the mouse are located both medially and ventrally within the ARC, in contrast to a predominantly lateral position in the rat ARC.

POMC-EGFP neurons in hypothalamic slices had a resting membrane potential of –40 to –45 mV and exhibited frequent spontaneous action potentials. The non-selective opioid agonist met-enkephalin (Met-Enk: 30 μM; Sigma) caused a rapid (35- 40 s), reversible hyperpolarization (10-20 mV) of the membrane potential of POMC cells (n=10) and prevented spontaneous action potential generation (Fig. 2a). In normal (2.5 mM K^+) Krebs buffer, the reversal-potential of the inwardly-rectifying opioid current was approximately –90mV, while in 6.5 mM K^+ Krebs the reversal-potential was shifted to approximately –60 mV (n=3: Fig. 2b). The μ opioid receptor (MOP-R) antagonist CTAP (1 μM; Phoenix Pharmaceuticals) completely prevented the current induced by Met-Enk in POMC cells (n=3: Fig. 2c). These characteristics indicate the opioid current was due to activation of MOP-R and increased ion conductance through G protein coupled, inwardly-rectifying

demonstrated co-localization of GABA and NPY (Horvath et al., *Brain Res* 756, 283-6, 1997) within subpopulations of ARC neurons, led us to speculate that leptin hyperpolarizes NPY/GABA cells that directly innervate POMC neurons, and thus reduces GABAergic drive onto POMC cells. Both the leptin and NPY Y2 receptors are expressed on NPY neurons in the ARC (Hakansson et al., *J Neurosci* 18, 559-72, 1998; Broberger et al., *Neuroendocrinology* 66, 393-408, 1997). Furthermore, activation of Y2 receptors inhibits NPY release from NPY neurons (King et al., *J Neurochem* 73, 641-6, 1999), and presumably would also diminish GABA release from NPY/GABA terminals. This is an alternative pharmacological approach, independent of leptin, to test the hypothesized innervation of POMC neurons by GABAergic NPY neurons. Indeed, NPY (100 nM; Bachem) decreased the frequency of GABAergic IPSCs by 55% within 3 minutes, in all 12 POMC cells tested (Fig. 4a). Both NPY and leptin still inhibited IPSCs in the presence of tetrodotoxin (TTX) (6 of 6 and 3 of 5 cells respectively), indicating that some of the inhibition of IPSCs was occurring through direct effects at presynaptic nerve terminals. POMC neurons express the NPY Y1 receptor (Broberger et al., *Neuroendocrinology* 66, 393-408, 1997) and NPY also hyperpolarized all POMC neurons tested, by an average of 9±6 mV (n=3).

Another pharmacological test to confirm the origin of GABAergic innervation on POMC neurons from NPY/GABA terminals was to test the effect of the recently characterized and highly selective MC3-R agonist D-Trp^8-γMSH (Grieco et al., *J Med Chem* 43, 4998-5002, 2000) on local GABA release. D-Trp^8-γMSH (7 nM) increased the frequency of GABAergic IPSCs (280 ± 90%) recorded from 3 of 4 POMC neurons (Fig. 4b). It had no effect on one cell. The positive effect of MC3-R activation, together with the negative effects of NPY and leptin, demonstrate the dynamic range of the NPY/GABA synapse onto POMC neurons and point to the important role of this synapse in modulating signal flow within the ARC. D-Trp^8-γMSH (7 nM) also hyperpolarized (-5.5 ± 2.4 mV) 9 of 15 POMC neurons tested and decreased the frequency of action potentials (Fig 4c); the remaining cells showed no significant response to D-Trp^8-γMSH. These effects could be due entirely to increased GABA release onto the POMC cells, or could be due to an additional postsynaptic action of D-Trp^8-γMSH on POMC neurons,

al., *Scand. J. Clin. Lab. Invest.* 56, 497-503, 1996). The effects of peripheral administration of PYY_{3-36} on feeding were investigated.

An intraperitoneal injection (IP) of PYY_{3-36} to freely feeding rats, prior to the onset of the dark-phase, significantly decreased subsequent food intake (Fig. 5a). A similar inhibition of feeding was seen following IP injection in rats fasted for 24 hours (Fig. 5b). A time course of the plasma PYY_{3-36} levels achieved following IP injection of PYY_{3-36} demonstrated a peak level at 15 minutes post injection, which was within the normal postprandial range (peak PYY_{3-36} levels 15 minutes post IP injection of 0.3μg/100g = 99.3 ± 10.4 pmol/l vs. peak postprandial level = 112.1 ± 7.8 pmol/l, n = 8-10 per group), suggesting that physiological concentrations of PYY_{3-36} inhibit feeding. PYY_{3-36} did not affect gastric emptying (percentage of food ingested remaining in the stomach at 3 hours: PYY_{3-36} = 36 ± 1.9 %, saline = 37.4 ± 1.0 % n = 12) (Barrachina et al., *Am. J. Physiol.* 272, R1007-11, 1997). PYY_{3-36} administered IP twice daily for 7 days reduced cumulative food intake (7-day cumulative food intake: PYY_{3-36} = 187.6 ± 2.7g vs. saline = 206.8 ± 2.3, n = 8 per group, $P < 0.0001$) and decreased body weight gain (Fig. 5d) (PYY_{3-36} = 48.2 ± 1.3g vs. saline = 58.7 ± 1.9, n = 8 per group, $P < 0.002$).

Example 4

PYY Administration Affects c-fos Expression

To investigate whether this inhibition of food intake involved a hypothalamic pathway, c-fos expression was examined in the arcuate nucleus, an important center of feeding control (Schwartz et al., *Nature* 404, 661-671, 2000; Cowley et al., *Nature* 411, 480-484, 2001), following a single IP injection of PYY_{3-36}. There was a 2-fold increase in the number of cells positive for c-fos in the lateral arcuate of the rat (PYY_{3-36} =168 ± 2, saline = 82.7 ± 5, n = 3, $P < 0.0001$). Likewise in *Pomc-EGFP*-transgenic mice (Cowley et al., *Nature* 411, 480-484, 2001) IP administration of PYY_{3-36} resulted in a 1.8-fold increase in the number of arcuate cells positive for c-fos (Fig. 6b), compared with saline control animals (Fig. 6a) (PYY_{3-36} = 250 ± 40, saline = 137 ± 15, n = 5, $P < 0.05$). IP PYY_{3-36} caused a 2.6 fold increase in the proportion of POMC neurons that express c-fos (PYY_{3-36} = 20.4 ± 2.9%, saline = 8 ± 1.4%, n = 5, $P < 0.006$) (Figs. 6c and d).

injection, 0.1 nmol Y2A = 6.2 ± 0.5 g, saline = 8.2 ± 0.6 g, n = 8 per group, P < 0.05).

To confirm the anatomical specificity of this effect Y2A (100 fmol - 1 nmol) was injected into the paraventricular nucleus (PVN) (Kim et al., *J. Clin. Invest.* 105, 1005-11, 2000) of rats fasted for 24 hours and found no alteration of food intake (2 hour post-injection saline = 8.3 ± 0.4 g, 0.1nmol Y2A = 8.0 ± 0.6 g, n = 8 per group). To further determine the role of the Y2R in the feeding inhibition caused by peripheral PYY_{3-36}, the effect of PYY_{3-36} on *Y2r*-null mice and littermate controls was examined. PYY_{3-36} inhibited daytime feeding in a dose responsive manner in fasted male wild-type mice but did not inhibit food intake in fasted male *Y2r*-null mice (Figs. 7b and 7c). Food intake measured in response to a fast demonstrated that male *Y2r*-null mice eat significantly more at 2, 4 and 24 hours compared with their littermate controls (24-hour cumulative food intake; *Y2r*-null mice = 7.1 ± 0.48g vs. wild-type = 5.3 ± 0.7g, n = 8 per group, P < 0.05).

The electrophysiological response of hypothalamic POMC neurons to administration of both PYY_{3-36} and Y2A was examined. These neurons were identified using mice with targeted expression of green fluorescent protein in POMC neurons (Cowley et al., *Nature* 411, 480-484, 2001). PYY_{3-36} disinhibited the POMC neurons, resulting in a significant depolarization of 19 of the 22 POMC neurons tested (Fig. 8a inset) (10.3 ± 2.1 mV depolarization, n = 22, P < 0.0003). A similar depolarization was seen with Y2A (8.7 ± 1.8 mV depolarization, n = 9, P < 0.002). The depolarization caused by PYY_{3-36} stimulated a significant increase in the frequency of action potentials in POMC neurons (Fig 8a) (93% increase over control, P < 0.05, n = 22). In the whole cell mode the effect of PYY_{3-36} was sometimes reversed upon washout, but only after a long latency (30 minutes). A similar washout of leptin effects upon these neurons was observed.

To exclude effects of cellular rundown, or seal deterioration, the effects of PYY_{3-36} in the "loose cell-attached" (or extracellular) configuration was examined. PYY_{3-36} caused a reversible 5-fold increase in the frequency of action potentials in loose cell-attached recordings of POMC neurons (Fig. 8b). This increase in firing rate occurred with the same latency as PYY_{3-36} reduced the frequency of inhibitory postsynaptic currents (IPSCs) onto all 13 POMC neurons tested (Fig. 8c) (51.9 ± 9.2

free-choice buffet meal (Tarling et al., *Intensive Care Med.* 23, 256-260, 1997) two hours after the termination of the infusion was reduced by over a third compared to saline (36 ± 7.4%, $p < 0.0001$) (Fig. 9a). There was no effect upon fluid intake and no difference in sensations of fullness or nausea reported by the volunteers. PYY_{3-36} administration had no effect on gastric emptying, as estimated by the paracetamol absorption method (Edwards et al., *Am. J. Physiol. Endocrinol. Metab.* 281, E155-E166, 2001; Tarling et al., *Intensive Care Med.* 23, 256-260, 1997), or on plasma glucose, plasma leptin, GLP-1, or insulin. Analysis of the food diaries revealed a significant inhibition of food intake in the 12-hour period following the PYY_{3-36} infusion (saline = 2205 ± 243 kcal, PYY_{3-36} = 1474 ± 207 kcal). However, food intake during a 12 to 24 hour period between the two groups was virtually identical. Overall there was a 33% decrease in cumulative total calorie consumption in the 24-hour period following the PYY_{3-36} infusion (Fig.9b). These findings demonstrate that infusion of PYY_{3-36}, matching postprandial levels, caused a marked inhibition of both appetite and food intake in man.

In an additional study, two groups of healthy subjects (n = 12 per group, 6 males and 6 females), one with increased Body Mass Index (BMI) (mean = 32.73 +/- 0.93 kg/m2) and another group with low BMI (mean = 20.49 +/- 2.05 kg/m2), were studied on two occasions with at least 1 week between each study. All subjects fasted and drank only water from 20:00 hours on the evening prior to each study. Subjects arrived at 08:30 on each study day, were cannulated and then allowed to relax for 30 minutes prior to the onset of the study protocol. Subjects were infused with either saline or 0.8 pmol.kg1.min-1 PYY_{3-36} for 90 minutes, in a double blind randomized crossover design. Two hours after the termination of the infusion, subjects were offered an excess free-choice buffet meal, such that all appetites could be satisfied. Food and water were weighed pre- and postprandially and caloric intake calculated. Caloric intake following saline and PYY_{3-36} were compared using a paired t test ($p<0.001$). The number of calories ingested following administration of PYY_{3-36} differed significantly from the number of calories ingested following administration of saline for both the overweight group and the lean group. The overweight group showed a 28.8 +/- 4.3 % reduction and the lean group a 31.1 +/- 4.4 % reduction. However, the reduction for the overweight group did not differ

described disclosure. We claim all such modifications and variations that fall within the scope and spirit of the claims below.

about 135 pmol per kilogram of body weight at least about 30 minutes prior to a meal.

10. The method of claim 1, further comprising administering a therapeutically effective amount of amfepramone (diethylpropion), phentermine, mazindol, phenylpropanolamine, fenfluramine, dexfenfluramine, or fluoxetine.

11. The method of claim 1, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease calorie intake for a period of at least about 2 hours.

12. The method of claim 11, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease calorie intake for a period of about 2 to 12 hours.

13. The method of claim 1, wherein the subject is human.

14. The method of claim 1, wherein the PYY agonist comprises a molecule that specifically binds the Y2 receptor.

15. The method of claim 14, wherein the PYY agonist increases the expression of c-fos in a section of an arcuate nucleus contacted with the compound.

16. The method of claim 1, wherein the PYY agonist specifically binds to a neuropeptide Y neuron and inhibits an activity of a neuropeptide Y neuron.

17. The method of claim 16, wherein the PYY agonist decreases the action potential firing rate of the neuropeptide Y neuron.

18. The method of claim 16, wherein the neuropeptide Y neuron synapses with a proopiomelanocortin neuron, and wherein binding of the PYY agonist to the

28. The method of claim 24, wherein peripherally administering the therapeutically effective amount of PYY or the agonist thereof comprises administering PYY or an agonist thereof to the subject in a multitude of doses, wherein each dose in the multitude of doses comprises administration of about 45 to about 135 pmol per kilogram of body weight at least about 30 minutes prior to a meal.

29. The method of claim 20, further comprising administering a therapeutically effective amount of amfepramone (diethylpropion), phentermine, mazindol, phenylpropanolamine, fenfluramine, dexfenfluramine, or fluoxetine.

30. The method of claim 20, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease calorie intake for a period of at least about 2 hours.

31. The method of claim 20, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease appetite for a period of about 2 to about 12 hours.

32. The method of claim 20, wherein the subject is human.

33. The method of claim 20, wherein the PYY agonist comprises a molecule that specifically binds the Y2 receptor.

34. The method of claim 20, wherein the PYY agonist increases the expression of c-fos in a section of an arcuate nucleus contacted with the compound.

35. The method of claim 20, wherein the PYY agonist specifically binds to a neuropeptide Y neuron and inhibits an activity of a neuropeptide Y neuron.

45. The method of claim 43, wherein peripherally administering PYY or the agonist thereof comprises administering about 72 pmol per kilogram body weight of the subject.

46. The method of claim 39, wherein peripherally administering PYY or the agonist thereof comprises administering about 45 to about 135 pmol per kilogram body weight of the subject at least 30 minutes prior to a meal.

47. The method of claim 39, wherein peripherally administering the therapeutically effective amount of PYY or the agonist thereof comprises administering PYY or an agonist thereof to the subject in a multitude of doses, wherein each dose in the multitude of doses comprises administration of about 0.5 to about 135 pmol per kilogram of body weight at least about 30 minutes prior to a meal.

48. The method of claim 39, further comprising administering a therapeutically effective amount of amfepramone (diethylpropion), phentermine, mazindol, phenylpropanolamine, fenfluramine, dexfenfluramine, or fluoxetine.

49. The method of claim 39, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease calorie intake at least about 2 hours.

50. The method of claim 39, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease food intake for about 2 to about 12 hours.

51. The method of claim 39, wherein the subject is human.

52. The method of claim 39, wherein the PYY agonist comprises a molecule that specifically binds the Y2 receptor.

63. The method of claim 62, wherein the pulse dose comprises about 72 pmol per kilogram body weight of the subject.

64. The method of claim 58, wherein the pulse dose is administered to the subject at least about 30 minutes prior to a meal.

65. The method of claim 58, further comprising administering a therapeutically effective amount of amfepramone (diethylpropion), phentermine, mazindol, phenylpropanolamine, fenfluramine, dexfenfluramine, or fluoxetine to the subject.

66. The method of claim 58, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease calorie intake for a period of at least about 2 hours.

67. The method of claim 58, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease calorie intake for a period of about 2 to about 12 hours.

68. The method of claim 58, wherein peripherally injecting comprises subcutaneous, intravenous, intramuscular, intranasal, transdermal or sublingual administration.

69. The method of claim 58, wherein peripherally injecting comprises intramuscular administration.

70. The method of claim 58, wherein the subject is human.

71. The method of claim 58, wherein the PYY agonist comprises a molecule that specifically binds the Y2 receptor.

82. The method of claim 81, wherein peripherally administering PYY or the agonist thereof comprises administering about 45 to about 135 pmol per kilogram body weight of the subject.

83. The method of claim 81, wherein peripherally administering PYY or the agonist thereof comprises administering about 72 pmol per kilogram body weight of the subject.

84. The method of claim 82, wherein peripherally administering PYY or the agonist thereof comprises administering about 35 to about 135 pmol per kilogram body weight of the subject at least 30 minutes prior to a meal.

85. The method of claim 77, wherein peripherally administering the therapeutically effective amount of PYY or the agonist thereof comprises administering PYY or an agonist thereof to the subject in a multitude of doses, wherein each dose in the multitude of doses comprises administration of about 0.5 to about 135 pmol per kilogram of body weight at least about 30 minutes prior to a meal.

86. The method of claim 77, further comprising administering a therapeutically effective amount of amfepramone (diethylpropion), phentermine, mazindol, phenylpropanolamine, fenfluramine, dexfenfluramine, or fluoxetine.

87. The method of claim 77, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease calorie intake for a period of at least about 2 hours.

88. The method of claim 77, wherein the PYY or the agonist thereof is administered in an amount sufficient to decrease food intake for a period of about 2 to about 12 hours.

98. The method of claim 39, wherein peripherally administering PYY or the agonist thereof comprises administering a dose sufficient to raise the serum level of PYY or the agonist thereof to a level of to effect a reduction in food intake equivalent to the reduction in food intake caused by a postprandial level of PYY_{3-36}.

99. The method of claim 98, wherein the postparandial level of PYY_{3-36} is from about 40 pM to about 50 pM.

100. The method of claim 58, wherein peripherally administering PYY or the agonist thereof comprises administering a dose sufficient to raise the serum level of PYY or the agonist thereof to a level of to effect a reduction in calorie intake, food intake, or appetite equivalent to the reduction in calorie intake, food intake, or appetite caused by a postprandial level of PYY_{3-36}.

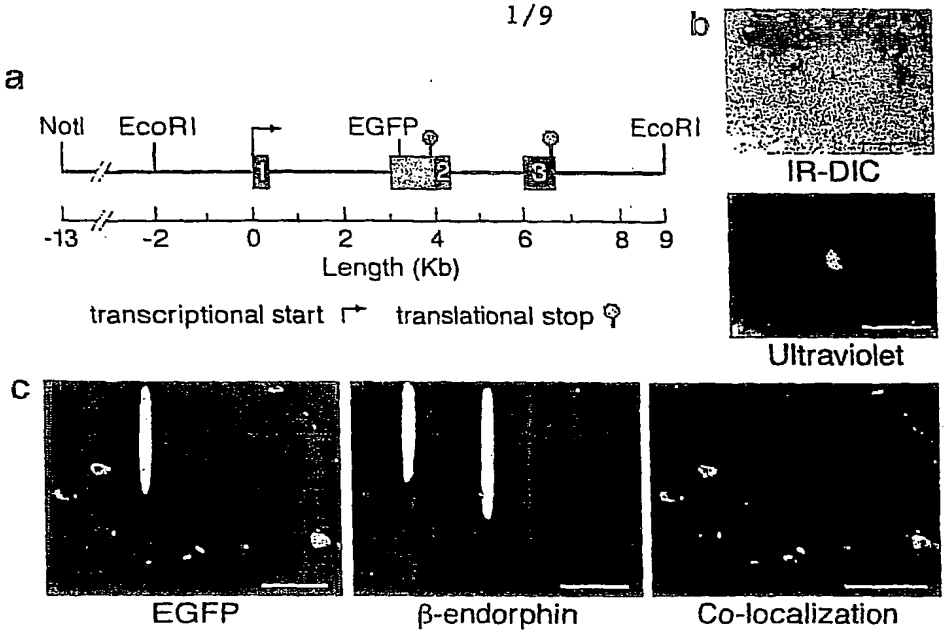
101. The method of claim 100, wherein the postparandial level of PY_{3-36} is from about 40 pM to about 50 pM.

100. The method of claim 77, wherein peripherally administering PYY or the agonist thereof comprises administering a dose sufficient to raise the serum level of PYY or the agonist thereof to a level of to effect an increase in energy expenditure equivalen to the increase in energy expenditure caused a postprandial level of PYY_{3-36}.

101. The method of claim 100, wherein the postparandial level of PYY_{3-36} is from about 40 pM to about 50 pM.

102. The method of any one of claims 1, 39, 58, 177, or 100, wherein PYY or an agonist thereof is PYY_{3-36}.

103. Use of PYY or an agonist thereof for the manufacture of a medicament for use in a method as claimed in any one of claims 1 to 101.


a
NotI
EcoRI
EGFP
EcoRI
1
2
3
-13
-2
0
2
4
6
8
9
Length (Kb)
transcriptional start
translational stop
b
IR-DIC
Ultraviolet
c
EGFP
β-endorphin
Co-localization

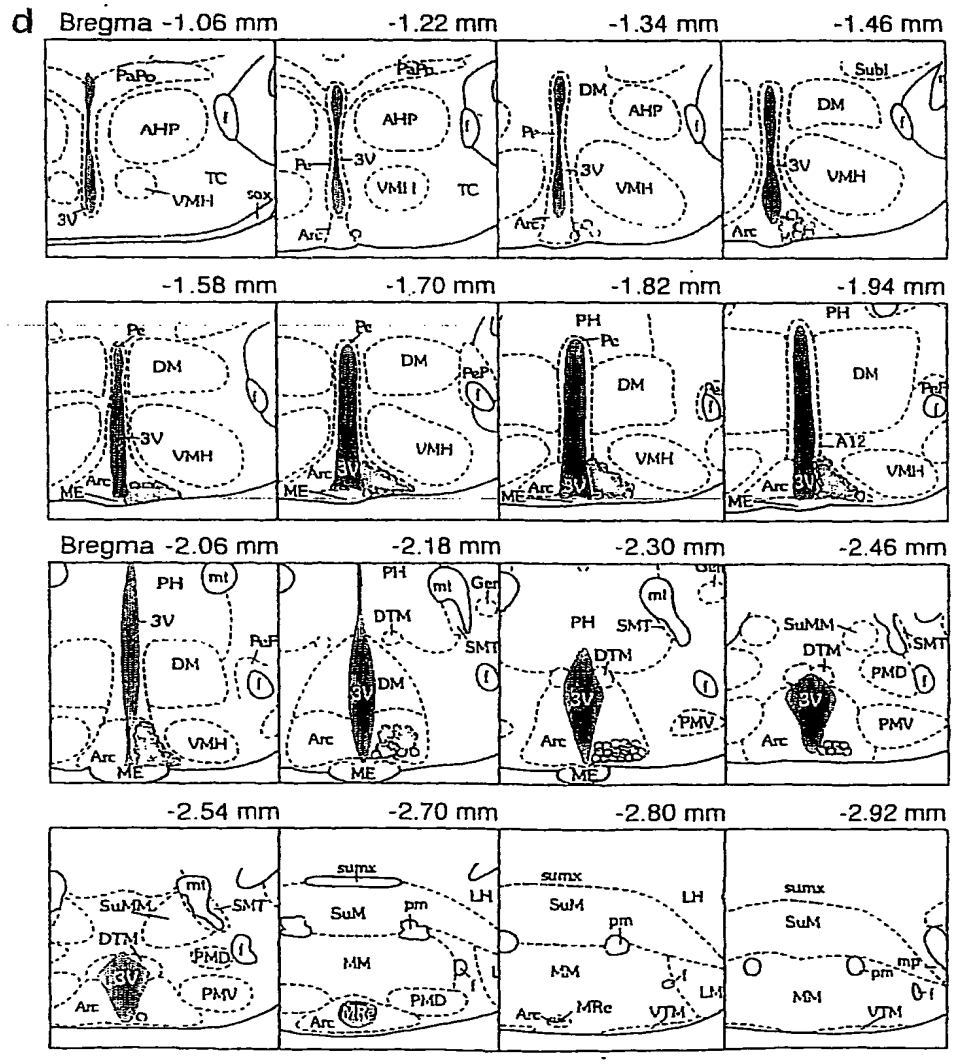

d
Bregma -1.06 mm
-1.22 mm
-1.34 mm
-1.46 mm
-1.58 mm
-1.70 mm
-1.82 mm
-1.94 mm
Bregma -2.06 mm
-2.18 mm
-2.30 mm
-2.46 mm
-2.54 mm
-2.70 mm
-2.80 mm
-2.92 mm
AHP
TC
VMH
3V
DM
PH
Arc
ME
SuM
LH
PMD
PMV
VTM

FIG. 1

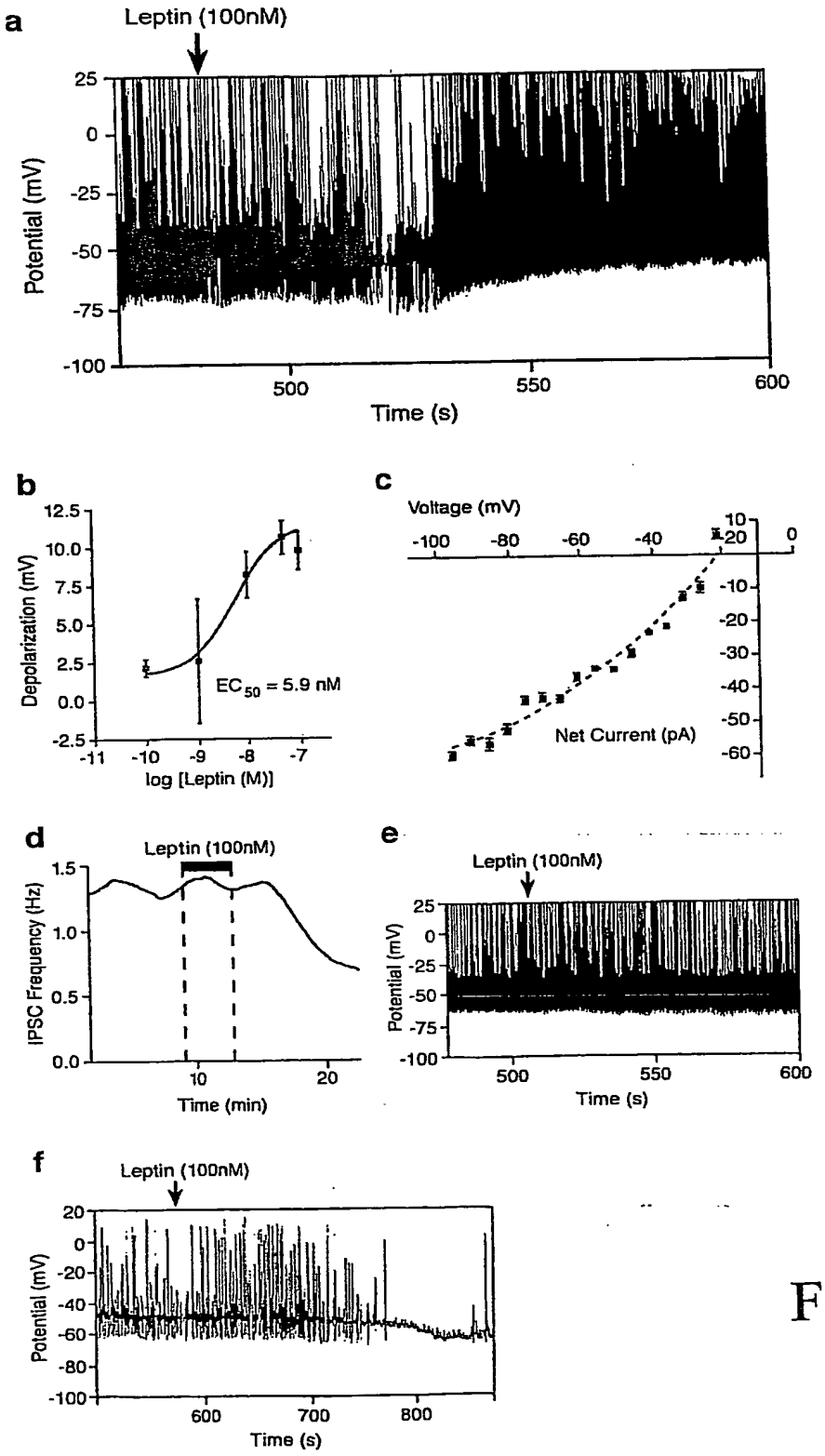

a
Leptin (100nM)
Potential (mV)
Time (s)
b
Depolarization (mV)
EC50 = 5.9 nM
log [Leptin (M)]
c
Voltage (mV)
Net Current (pA)
d
Leptin (100nM)
IPSC Frequency (Hz)
Time (min)
e
Leptin (100nM)
Potential (mV)
Time (s)
f
Leptin (100nM)
Potential (mV)
Time (s)

FIG. 3

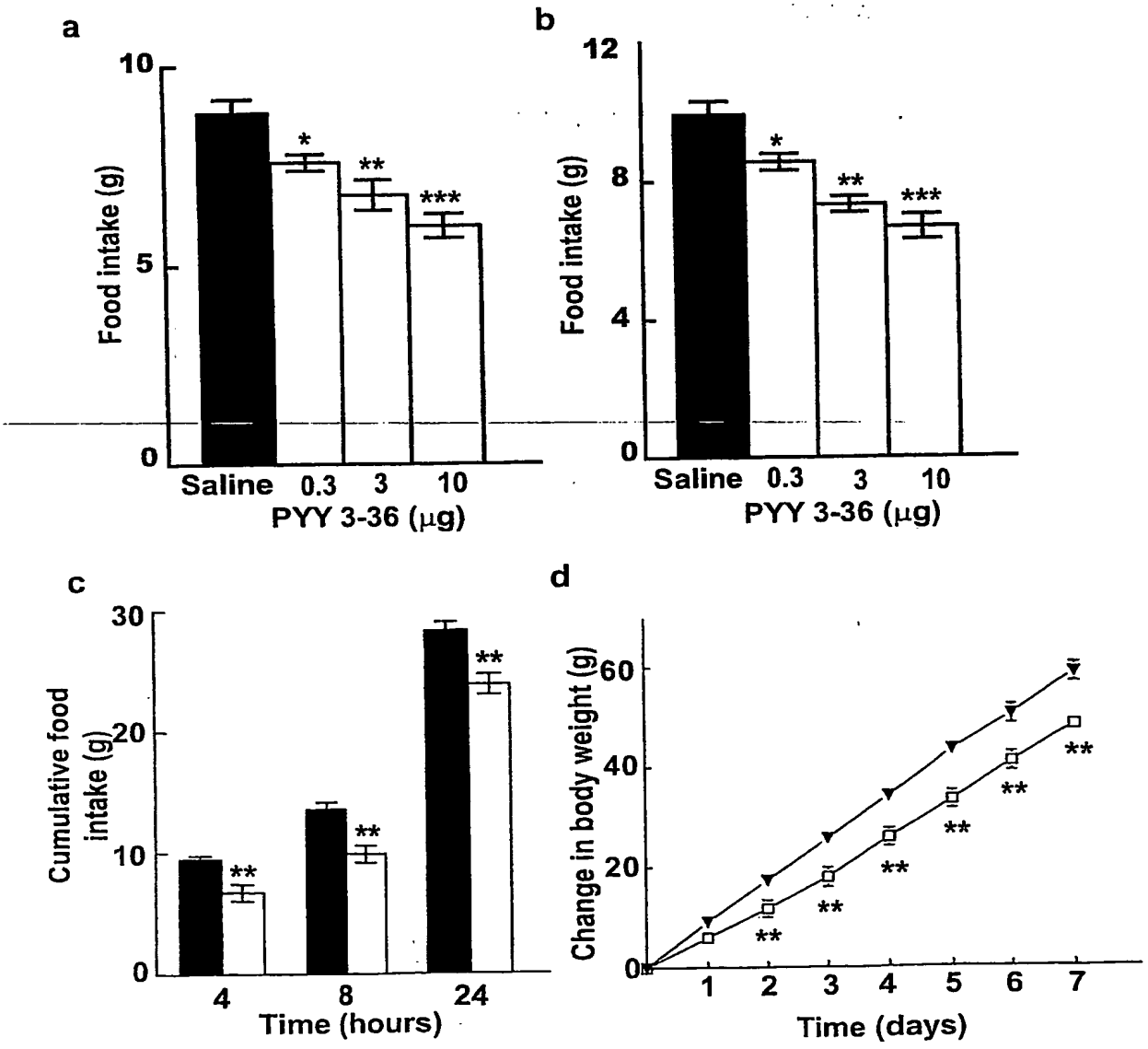

a
Food intake (g)
10
5
0
*
**
***
Saline
0.3
3
10
PYY 3-36 (μg)
b
Food intake (g)
12
8
4
0
*
**
***
Saline
0.3
3
10
PYY 3-36 (μg)
c
Cumulative food intake (g)
30
20
10
0
**
**
**
4
8
24
Time (hours)
d
Change in body weight (g)
60
40
20
0
**
**
**
**
**
1
2
3
4
5
6
7
Time (days)

FIG. 5

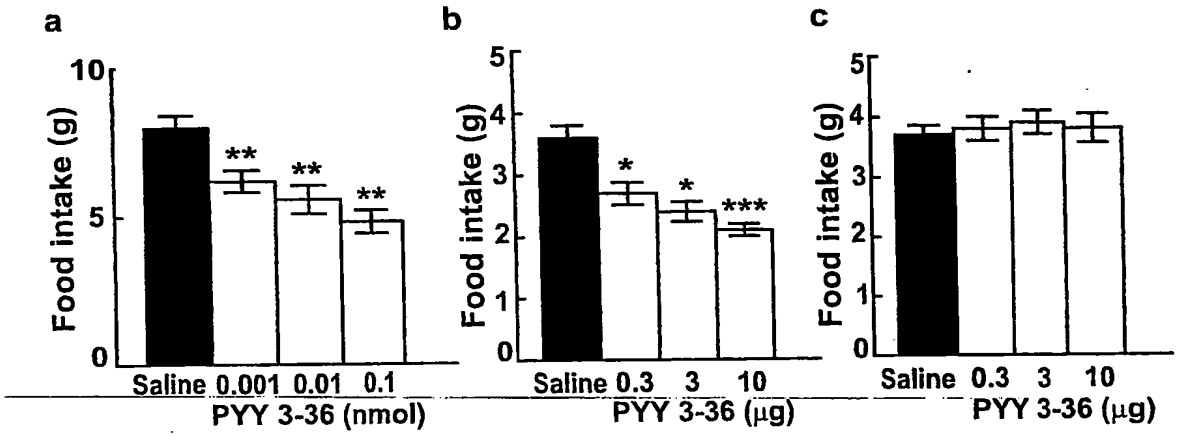

a
b
c
Food intake (g)
10
5
0
5
4
3
2
1
0
**
**
**
*
*
***
Saline 0.001 0.01 0.1
PYY 3-36 (nmol)
Saline 0.3 3 10
PYY 3-36 (μg)
Saline 0.3 3 10
PYY 3-36 (μg)

FIG. 7

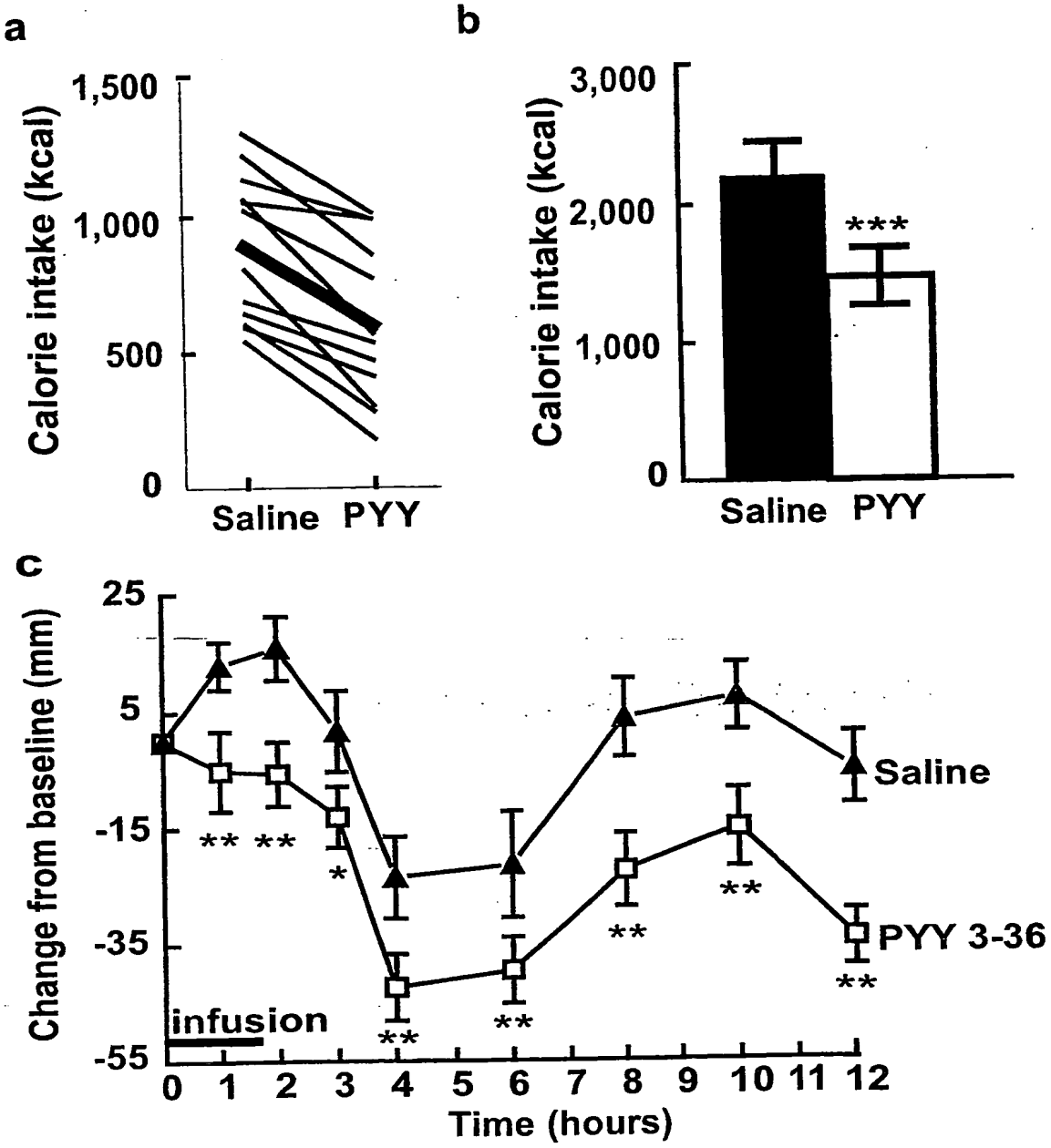

a
b
c
Calorie intake (kcal)
1,500
1,000
500
0
Saline PYY
3,000
2,000
1,000
***
Change from baseline (mm)
25
5
-15
-35
-55
infusion
Saline
PYY 3-36
Time (hours)
0 1 2 3 4 5 6 7 8 9 10 11 12

FIG. 9

Met Ala Gln Tyr Ala Ala Glu Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 4
<211> 3
<212> PRT
<213> Homo sapiens

<400> 4

000
1

<210> 5
<211> 36
<212> PRT
<213> Rattus sp.

<400> 5

Tyr Pro Ala Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Ser Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 6
<211> 36
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<213> Sus sp.

<400> 6

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1 5 10 15

Leu Ser Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 7
<211> 36
<212> PRT
<213> Cavia porcellus

<400> 7

Tyr Pro Ser Lys Pro Glu Ala Pro Gly Ser Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Ala Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

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<211> 36
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<213> Petromyzontidae gen. sp.

<400> 12

Met Pro Pro Lys Pro Asp Asn Pro Ser Pro Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Ser Lys Tyr Met Leu Ala Val Arg Asn Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 13
<211> 36
<212> PRT
<213> Rattus sp.

<400> 13

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 14
<211> 36
<212> PRT
<213> Oryctolagus cuniculus

<400> 14

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 15
<211> 36
<212> PRT
<213> Canis familiaris

<400> 15

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 20
<211> 36
<212> PRT
<213> Avian

<400> 20

Tyr Pro Ser Lys Pro Asp Ser Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 21
<211> 36
<212> PRT
<213> Rana sp.

<400> 21

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Lys Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 22
<211> 36
<212> PRT
<213> Carassius auratus

<400> 22

Tyr Pro Thr Lys Pro Asp Asn Pro Gly Glu Gly Ala Pro Ala Glu Glu
1 5 10 15

Leu Ala Lys Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 23
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<213> Dogfish sp.

<400> 23

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Gly Ala Pro Ala Glu Asp
1 5 10 15

Leu Ala Lys Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 28
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<213> Felis catus

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Ala Pro Leu Glu Pro Val Tyr Pro Gly Asp Asn Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Ala Ala Glu Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 29
<211> 36
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<213> Bos taurus

<400> 29

Ala Pro Leu Glu Pro Glu Tyr Pro Gly Asp Asn Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Ala Ala Glu Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 30
<211> 36
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<213> Rattus sp.

<400> 30

Ala Pro Leu Glu Pro Met Tyr Pro Gly Asp Tyr Ala Thr His Glu Gln
1 5 10 15

Arg Ala Gln Tyr Glu Thr Gln Leu Arg Arg Tyr Ile Asn Thr Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 31
<211> 36
<212> PRT
<213> Mus musculus

<400> 31

Ala Pro Leu Glu Pro Met Tyr Pro Gly Asp Tyr Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Glu Thr Gln Leu Arg Arg Tyr Ile Asn Thr Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 36
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Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

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Arg His Thr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

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<213> Artificial Sequence

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Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

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Arg His Tyr Ile Asn Leu Val Thr Arg Gln Arg Tyr
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1 5 10

<210> 46
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Arg His Tyr Leu Asn Leu Val Ser Arg Gln Arg Tyr
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<210> 47
<211> 12
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Arg His Tyr Leu Asn Leu Val Thr Lys Gln Arg Tyr
1 5 10

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<211> 12
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Arg His Tyr Leu Asn Leu Val Thr Arg Asn Arg Tyr
1 5 10

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<400> 49

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Lys Tyr
1 5 10

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Lys His Tyr Val Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 56
<211> 12
<212> PRT
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<400> 56

Lys His Tyr Leu Gln Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 57
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Lys His Tyr Leu Asn Ile Val Thr Arg Gln Arg Tyr
1 5 10

<210> 58
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Lys His Tyr Leu Asn Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 60
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<213> Artificial Sequence

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<210> 66
<211> 12
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<400> 66

Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Phe
1 5 10

<210> 67
<211> 12
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Arg His Thr Ile Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 68
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<220>
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<400> 68

Arg His Thr Val Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 69
<211> 12
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1 5 10

<210> 70

<210> 75
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1 5 10

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<220>
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<400> 76

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1 5 10

<210> 77
<211> 12
<212> PRT
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<220>
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<400> 77

Arg His Thr Leu Asn Leu Val Thr Arg Gln Lys Tyr
1 5 10

<210> 78
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1 5 10

<210> 79
<211> 12
<212> PRT
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<220>
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1 5 10

Arg His Phe Leu Asn Val Val Thr Arg Gln Arg Tyr
1 5 10

<210> 85
<211> 12
<212> PRT
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<220>
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1 5 10

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<220>
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<400> 86

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1 5 10

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1 5 10

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Arg His Phe Leu Asn Leu Val Thr Lys Gln Arg Tyr
1 5 10

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1 5 10

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<220>
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1 5 10

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Arg His Tyr Leu Gln Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 97
<211> 12
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<400> 97

Arg His Tyr Leu Gln Leu Val Ser Arg Gln Arg Tyr
1 5 10

<210> 98
<211> 12
<212> PRT
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<220>
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<400> 98

Arg His Tyr Leu Gln Leu Val Thr Lys Gln Arg Tyr
1 5 10

<210> 99
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<212> PRT
<213> Artificial Sequence

<220>
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1 5 10

<210> 105
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<220>
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<400> 105

Arg His Tyr Leu Asn Ile Val Ser Arg Gln Arg Tyr
1 5 10

<210> 106
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<400> 106

Arg His Tyr Leu Asn Ile Val Thr Lys Gln Arg Tyr
1 5 10

<210> 107
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<400> 107

Arg His Tyr Leu Asn Ile Val Thr Arg Asn Arg Tyr
1 5 10

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<400> 108

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1 5 10

<210> 109

<210> 114
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<220>
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<400> 114

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1 5 10

<210> 115
<211> 12
<212> PRT
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<220>
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<400> 115

Arg His Tyr Leu Asn Val Val Thr Arg Asn Arg Tyr
1 5 10

<210> 116
<211> 12
<212> PRT
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<220>
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<400> 116

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1 5 10

<210> 117
<211> 12
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<400> 117

Arg His Tyr Leu Asn Val Val Thr Arg Gln Arg Thr
1 5 10

<210> 118
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<220>
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<400> 118

Arg His Tyr Leu Asn Val Val Thr Arg Gln Arg Phe
1 5 10

Arg His Tyr Leu Asn Leu Ile Thr Arg Gln Arg Thr
1 5 10

<210> 124
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<400> 124

Arg His Tyr Leu Asn Leu Ile Thr Arg Gln Arg Phe
1 5 10

<210> 125
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<400> 125

Arg His Tyr Leu Asn Leu Leu Ser Arg Gln Arg Tyr
1 5 10

<210> 126
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 126

Arg His Tyr Leu Asn Leu Leu Thr Lys Gln Arg Tyr
1 5 10

<210> 127
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 127

Arg His Tyr Leu Asn Leu Leu Thr Arg Asn Arg Tyr
1 5 10

<210> 128
<211> 12
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<220>
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<223> Polypeptide variation

<400> 133

Arg His Tyr Leu Asn Leu Val Ser Arg Gln Lys Tyr
1 5 10

<210> 134
<211> 12
<212> PRT
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<220>
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<400> 134

Arg His Tyr Leu Asn Leu Val Ser Arg Gln Arg Thr
1 5 10

<210> 135
<211> 12
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<220>
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<400> 135

Arg His Tyr Leu Asn Leu Val Ser Arg Gln Arg Tyr
1 5 10

<210> 136
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<400> 136

Arg His Tyr Leu Asn Leu Val Thr Lys Asn Arg Tyr
1 5 10

<210> 137
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 137

Arg His Tyr Leu Asn Leu Val Thr Lys Gln Lys Tyr
1 5 10

<210> 138
<211> 12
<212> PRT
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<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 143

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Lys Thr
1 5 10

<210> 144
<211> 12
<212> PRT
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<220>
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<400> 144

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Lys Phe
1 5 10

<210> 145
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 145

Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 146
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<400> 146
Ile Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 147
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<400> 147

Val Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 148

<210> 153
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 153

Thr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 154
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 154

Phe Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 155
<211> 17
<212> PRT
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<220>
<223> Polypeptide variation

<400> 155

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
1 5 10 15

Tyr

<210> 156
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 156

Thr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
1 5 10 15

Tyr

<210> 157
<211> 17
<212> PRT
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<220>
<223> Polypeptide variation

1 5 10 15

Gln Arg Tyr

<210> 162
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 162

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 163
<211> 20
<212> PRT
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<220>
<223> Polypeptide variation

<400> 163

Ile Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 164
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 164

Val Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 165
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 165

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
1 5 10 15

Leu Val Thr Arg Gln Arg Tyr
20

<210> 170
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<400> 170

Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu
1 5 10 15

Asn Leu Val Thr Arg Gln Arg Tyr
20

<210> 171
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 171

Thr Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu
1 5 10 15

Asn Leu Val Thr Arg Gln Arg Tyr
20

<210> 172
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
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<400> 172

Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr
1 5 10 15

Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 173
<211> 25
<212> PRT
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<220>
<223> Polypeptide variation

<400> 173

Ser Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr
1 5 10 15

His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 178
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 178

Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu
1 5 10 15

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 179
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 179

Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser
1 5 10 15

Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 180
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 180

Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala
1 5 10 15

Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 181
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 181

Ser Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala
1 5 10 15

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 186
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 186

Arg Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 187
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 187

Gln Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 188
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 188

Asn Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 189
<211> 34

<220>
<223> Polypeptide variation

<400> 193

Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 194
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 194

Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 195
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 195

Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg
1 5 10 15

Tyr

<210> 196
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 196

Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln
1 5 10 15

Arg Tyr

<210> 197
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 197

Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg
1 5 10 15

Leu Val Thr Arg Gln Arg Tyr
20

<210> 202
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 202

Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn
1 5 10 15

Leu Val Thr Arg Gln Arg Tyr
20

<210> 203
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 203

Ala Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu
1 5 10 15

Asn Leu Val Thr Arg Gln Arg Tyr
20

<210> 204
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 204

Asp Ala Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr
1 5 10 15

Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 205
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 205

Glu Asp Ala Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His
1 5 10 15

Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 210
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 210

Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr
1 5 10 15

Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 211
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 211

Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Glu Glu Leu Asn Arg Tyr
1 5 10 15

Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 212
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 212

Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 213
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 217

Leu Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 218
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 218

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 219
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 219

Ala Arg Tyr Tyr Ser Ala Leu Arg His Phe Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

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<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 222

Xaa Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 223
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> D Ser

<220>
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<222> (19)..(19)
<223> AMIDATION

<400> 223

Xaa Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 224
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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Arg Gln Arg Tyr
20

<210> 227
<211> 18
<212> PRT
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<222> (18)..(18)
<223> AMIDATION

<400> 227

Gln Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln
1 5 10 15

Arg Tyr

<210> 228
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 228

Ala Arg Phe Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 229
<211> 20
<212> PRT
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<222> (19)..(19)
<223> AMIDATION

<400> 231

Xaa Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 232
<211> 19
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<220>
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<220>
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<222> (1)..(1)
<223> FORMYLATION

<400> 232

Ala Arg Tyr Tyr Ser Glu Leu Arg Arg Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 233
<211> 20
<212> PRT
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<220>
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<222> (1)..(1)
<223> N terminus is bonded to H

<220>
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<222> (20)..(20)
<223> AMIDATION

<400> 233

Xaa Ala Arg Tyr Ala Ser Ala Leu Arg His Tyr Leu Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<220>
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<223> N terminus is bonded to H

<220>
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<222> (19)..(19)
<223> AMIDATION

<400> 236

Ala Arg Tyr Tyr Asp Ser Leu Arg His Tyr Ile Asn Thr Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 237
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> N terminus is bonded to H

<220>
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<222> (19)..(19)
<223> AMIDATION

<400> 237

Ala Arg Tyr Tyr Ser Ala Leu Gln His Tyr Ile Asn Leu Leu Thr Arg
1 5 10 15

Pro Arg Tyr

<210> 238
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 238

Leu Ala Arg Tyr Tyr Ser Ala Leu Arg Gln Tyr Arg Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Phe

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 241

Ser Arg Tyr Tyr Ala Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 242
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 242

Xaa Ala Arg Tyr Tyr Asn Ala Leu Arg His Phe Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 243
<211> 19
<212> PRT
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<220>
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<220>
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<223> N terminus is bonded to H

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<223> D Ala

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 246

Xaa Arg Tyr Tyr Ser Ala Leu Arg His Tyr Val Asn Leu Ile Phe Arg
1 5 10 15

Gln Arg Tyr

<210> 247
<211> 18
<212> PRT
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<220>
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<223> MeSer

<220>
<221> MOD_RES
<222> (18)..(18)
<223> AMIDATION

<400> 247

Xaa Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Met Ile Thr Arg Gln
1 5 10 15

Arg Phe

<210> 248
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<222> (19)..(19)
<223> AMIDATION

<400> 251

Xaa Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Phe

<210> 252
<211> 20
<212> PRT
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<220>
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<222> (20)..(20)
<223> AMIDATION

<400> 252

Met Ala Arg Tyr Tyr Ser Asp Leu Arg Arg Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 253
<211> 19
<212> PRT
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<222> (19)..(19)

<400> 256

Tyr Pro Ala Lys Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu
1 5 10 15

Ser Thr Tyr Tyr Ala Ser Leu Arg Xaa Tyr Leu Asn Leu Val Thr Arg
20 25 30

Glx Arg Tyr
35

<210> 257
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (15)..(15)
<223> AMIDATION

<400> 257

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 258
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
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<222> (15)..(15)
<223> AMIDATION

<400> 258

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Ala Arg Gln Arg Tyr
1 5 10 15

<210> 259
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 259

Ala Ala Leu Arg His Tyr Leu Asn Leu Val Ala Arg Gln Arg Tyr
1 5 10 15

<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 262

Ala Ser Leu Arg Xaa Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 263
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<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 263

Ala Ser Leu Arg His Tyr Glu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 264
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<220>
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<223> AMIDATION

<220>
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<222> (15)..(15)
<223> Xaa is N Me Tyr

<400> 264

Ala Ser Leu Arg His Phe Glu Asn Leu Val Thr Arg Gln Arg Xaa
1 5 10 15

<210> 265
<211> 15
<212> PRT
<213> Artificial Sequence

<222> (15)..(15)
<223> AMIDATION

<400> 267

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 268
<211> 15
<212> PRT
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<220>
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<220>
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<220>
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<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa is Ornithine

<400> 268

Ala Ser Leu Arg His Phe Glu Asn Leu Val Thr Arg Xaa Arg Xaa
1 5 10 15

<210> 269
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 269

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 270

<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 3 benzothienyalanine

<400> 272

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 273
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 3 benzothienyalanine

<400> 273

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 274
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 274

Ala Ser Leu Arg His Trp Leu Asn Leu Val Thr Arg Gln Arg Tyr

<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is tetrahydroisoquinoline

<400> 277

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 278
<211> 3
<212> PRT
<213> Homo sapiens

<400> 278

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1

<210> 279
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (11)..(11)
<223> AMIDATION

<400> 279

His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 280
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MOD_RES

Ala Ser Leu Arg His Xaa Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 283
<211> 3
<212> PRT
<213> Homo sapiens

<400> 283

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1

<210> 284
<211> 3
<212> PRT
<213> Homo sapiens

<400> 284

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1

<210> 285
<211> 3
<212> PRT
<213> Homo sapiens

<400> 285

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1

<210> 286
<211> 3
<212> PRT
<213> Homo sapiens

<400> 286

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<210> 287
<211> 3
<212> PRT
<213> Homo sapiens

<400> 287

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1

<210> 288
<211> 3
<212> PRT
<213> Homo sapiens

<400> 288

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<400> 291

Ala Ser Leu Arg His Tyr Trp Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 292
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 292

Ala Ser Leu Arg His Tyr Leu Asn Trp Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 293
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 293

Ala Ser Leu Arg Ala Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 294
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa is D form of Trp

<220>
<221> MOD_RES
<222> (11)..(11)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (11)..(11)
<223> N alpha ACETYLATION

<400> 297

Ala Ser Leu Arg His Phe Leu Asn Leu Val Xaa Arg Gln Arg Tyr
1 5 10 15

<210> 298
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (13)..(13)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to CH3CO

<400> 298

Leu Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 299
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (13)..(13)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to CH3CO

<400> 299

<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is Norleucine

<400> 302

Ala Ser Xaa Arg His Trp Xaa Asn Xaa Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 303
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>

<400> 304

Ala Ser Xaa Arg His Phe Xaa Asn Xaa Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 305
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<400> 305

Ala Ser Xaa Arg His Phe Xaa Asn Trp Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 306
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a psuedopeptide bond consisting of CH2 NH2

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<400> 308

Ala Ser Leu Arg His Tyr Xaa Asn Trp Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 309
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH2

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH2

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<400> 309

Ala Ser Xaa Arg His Tyr Xaa Asn Trp Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<220>
<221> DISULFID
<222> (1)..(1)
<223> sequence is linked to an identical sequence

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<400> 312

Cys Tyr Arg Leu Arg Tyr
1 5

<210> 313
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MISC_FEATURE
<222> (3)..(4)
<223> Connected by NH CH CO

<220>
<221> MISC_FEATURE
<222> (3)..(4)
<223> Identical peptide chains are connected by (CH2)4 at the CH o
f NH CH CO

<400> 313

Ile Asn Pro Tyr Arg Leu Arg Tyr
1 5

<210> 314
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> C terminus is bonded to OCH3

<400> 314

Tyr Arg Leu Arg Tyr Tyr Arg Leu Arg Tyr
1 5 10

Tyr Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5 10

<210> 319
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 319

His Tyr Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5 10

<210> 320
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 320

Arg His Tyr Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5 10

<210> 321
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 321

Tyr Ile Asn Leu Leu Tyr Arg Gln Arg Tyr
1 5 10

<210> 322
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is 6 amino hexanoic acid

<400> 322

Tyr Pro Ser Leu Xaa Tyr Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5 10 15

<210> 323
<211> 9

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminal is bonded to H

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 326

Ala Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 327
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (9)..(9)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<400> 327

Ala Ser Leu Arg Thr Arg Gln Arg Tyr
1 5

<210> 328
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 2 thienylalanine

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 328

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 333

His Pro Phe His Leu
1 5

<210> 334
<211> 34
<212> PRT
<213> Homo sapiens

<400> 334

Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
1 5 10 15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 335
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 335

Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp Met Ala
1 5 10 15

Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln
20 25 30

Arg Tyr